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A DISCUSSION OF CONTROVERSIAL POINTS IN AMPUTATION SURGERY

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THERE is great difference of opinion between surgeons concerning the various procedures of amputation surgery. Some disagree concerning only minor variations in technique or unimportant matters of personal preference; others differ in matters of basic importance. In time of war, because amputation is frequently necessary after severe injuries from high velocity missiles, great experience is gained in this field of surgery.

At Percy Jones General Hospital in the 33 month period from January, 1943, to October, 1945, the amputation service has cared for 2,783 patients with major amputations. This is a greater number of amputees than was cared for by the entire Medical Department of the United States Army during World War I, which produced only 2,635 amputees. These 2,783 patients had a total of 2,988 amputated extremities. The incidence of amputation per patient and the location of the extremities which were lost are presented in Table I.

As a result of this experience many procedures and techniques of amputation surgery which are controversial have been observed. Observation of this group of patients has established that certain methods have a definite value, while others give less favorable results.

OPEN CIRCULAR AMPUTATION

In the United States Army Medical Corps the open circular amputation, or as it is more commonly and less accurately termed, guillotine amputation, was mandatory in all instances of amputation for trauma in forward installations. In this type open operation the skin is cut circularly at the lowest level of good tissue and allowed to retract. The fascia is then incised at the line of skin retraction and the superficial muscles are sectioned and allowed to retract. The deeper muscles are then sectioned at the line of retraction of the superficial muscles and allowed to retract. The bone is then cut through at the line of muscle retraction. *The leg is not chopped off as if by a cleaver.* This procedure carried out

TABLE I.—AMPUTATIONS IN 2783 PATIENTS

	Cases	Per cent
1. Loss of 1 extremity only	2584	93
2. Loss of 2 extremities	194	6.9
3. Loss of 3 extremities	4	.14
4. Loss of 4 extremities	1	.03

SITE OF AMPUTATION

Lower extremity—(85%)	No.	Per cent
1. Hip disarticulation	7	.02
2. Above knee	1049	35.0
3. Below knee	1487	49.8
Upper extremity—(15%)		
1. Above elbow	203	6.7
2. Below elbow	243	6.8

correctly produces a potentially inverted cone when traction is applied to the skin, but leaves no flaps to trap infection. If the patient is given proper postoperative care, the essential of which is traction, the stump is usually ready for definitive surgery in 8 weeks. If constant traction is not applied muscles retract and a large section of bone protrudes from the end of the stump (Figs. 1 to 4).

The flap type of open operation in which overhanging duck bill flaps are produced was forbidden in the American Army forward hospitals. The British Army permitted its surgeons to do the so called flap guillotine operation, as they deemed it advisable. Many American surgeons, both in military and civilian practice, have taken exception to the absolute deletion of the flap type operation in forward hospitals and there has been considerable heated debate around this point. It was claimed that it was out of the question to keep traction on the open circular amputation, and that stumps resulting from this type of open operation would arrive in poor condition in the Zone of the Interior. This objection was not valid. In 3 years and in 2,783 patients with 2,988 stumps, there were 30 stumps, or 1 per cent, which had not had the proper postoperative care by the time they arrived at this Midwestern hospital. Many of these patients arrived at the Zone of Interior hospital with effective traction still on the stump, having crossed half of Europe, the Atlantic or Pacific Ocean, and half of this country, with very ingenious combinations of adhesive tape, plaster, and elastic bands to keep the skin from retracting.

The only valid arguments for the flap type of open operation are: (1) time, (2) the avoidance of a second operation. The argument of time is valid, in that if the immediate convalescence is not complicated by severe sepsis, early secondary closure is possible. In some instances after the first 10 days to 2 weeks the flaps can be permitted to fall together and be loosely sutured, thus obtaining a closed stump soon after the injury. The second point is not a valid argument in very many instances. A high percentage of amputation stumps resulting from the secondary closure of inaccurately cut flaps will be poor stumps, with too much redundant skin and muscle at their ends. This condition will require a late secondary operative procedure to produce the ideal stump. A young, vigorous man is going to, and must, use his prosthesis hard. He cannot get by with a poorly tailored stump. For the aged individual, who will probably use a prosthesis very occasionally and in whom the avoidance of surgical incidents is desirable, the flap type open operation may have added merit. For the young in whom perfection of stump is desired, the open circular amputation is believed superior, as in this method a late definitive operation is an accepted fact.

In amputations done for trauma, the danger of ever present infection becoming invasive and virulent is reduced to an absolute minimum by the perfect drainage afforded by the open circular operation. The definitive surgery to complete the closure of an open circular amputation is in effect a "late secondary wound closure." Whether it be accomplished by plastic closure or by reamputation at site of election, it is associated with very little danger. In carrying out the definitive or final operation in 2,988 stumps in 2,783 patients, who had had an open circular amputation, a severe recrudescence of infection in the amputated extremity as manifested by cellulitis; abscess, high febrile reaction and general sepsis, occurred in only 20 instances, or 0.66 per cent. No patient died as a result of the definitive surgery on the guillotine stump.

Five per cent of patients had some complication of their final surgery. The common complications were a mildly infected hematoma in the stump without systemic reaction, or a marginal skin necrosis; which required a minor skin plastic later. Most of the patients with the complication of hematoma on its evacuation after the removal of a few stitches recovered with a satisfactory stump and without further surgery.

The severe infections resulting from secondary closure or reamputation occurred many times where they were least anticipated. Some were in a stump which had been completely healed for many months or had been covered by a skin graft for many months. Other stumps which had more than a reasonable amount of granulation tissue at their

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 1. Open circular amputation, immediately postoperative.

Fig. 2. Open circular below knee amputation, 8 weeks postoperative. Turned back stockinette is for skin traction. As result of continuous traction, this stump is now ready for final operation. Skin is pulled well down over end of stump which is healed by scar contracture.

Fig. 3. Below knee stump, which has not had traction postoperatively. Skin has retracted and 5 centimeters of bone protrudes, which will have to be sacrificed.

end at the time of surgical revision convalesced with no reaction. The only inference to draw from this is that regardless of how nearly normal the condition of previously infected tissues may appear, it is never free of bacteria, and those bacteria may become rampant at any time.

All patients received for 48 hours prior to surgery either sulfonamides or penicillin systemically. They also received one or the other of these antibiotics for as long postoperatively as was indicated by their general condition or the local condition of the operative site. Sulfadiazine was the sulfonamide used. About 1,800 patients received sulfadiazine and 1000 penicillin. The patients preferred sulfadiazine to escape being punctured with a needle. One seemed about as effective as the other in this type of surgery, and a positive stand for either to the exclusion of the other was impossible. One or the other, however, should be used. In 500 operations, sulfonamides were used topically in the stump. Late in 1943 the topical use of sulfanilamides was discontinued. Since discontinuing the topical use of sulfonamides, the stumps healed better, with less reaction and less hematoma.

TECHNIQUE OF AMPUTATION

Opinion differs greatly regarding the actual technical steps of performing an amputation. As one reads surgical treatises on this subject,

Fig. 4. Method of applying skin traction to open circular amputation. The stockinette is glued to the skin before patient leaves the operating table and traction is started immediately.

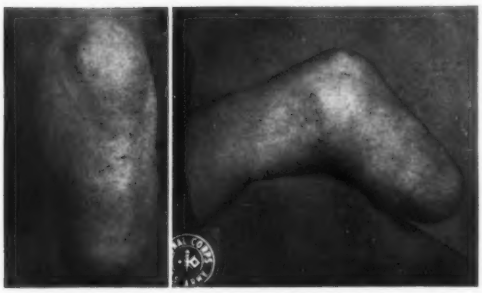


Fig. 5. a, left, Anteroposterior view. b, Lateral view. Good tapered below knee stump. Skin, nonadherent; no bulbous muscle over end; no bony prominences; no superficial neuromas.

the impression cannot be escaped that much has been carried through the years, from book to book, which does not hold in the light of present physiological and pathological fact.

The surgical technique of amputation should aim to produce a stump which has soft flexible, nonadherent skin, and which has no redundant muscle. There should result no projecting bony prominences and the neuromas of all nerves should be well covered and not subject to pressure.

In order to avoid adherent skin, dissection of the skin flap in the subcutaneous plane must be avoided as much as possible. A certain amount of freeing of the skin to effect a smooth closure is necessary but this rarely needs to exceed 3 centimeters from the skin flap's distal end. As nearly as possible the skin should be left attached to the fascia.

Wherever possible fascia should be closed over the bone end. In many instances of secondary closure this is impossible. Either fascia and skin or skin alone should be the only covering of the bone end. Muscle should never be used to cover the bone end as it results in a redundant unattached sliding mass at the end of the stump which shrinks very slowly and ultimately turns to scarred avascular tissue. All muscle should be coned out at least perpendicular to the bone end and, preferably, with its periphery slightly proximal to the bone end. Even in the avascular stump the presence of excess muscle in no way aids the skin circulation, as there are no perforating arteries between muscle and skin.

Some controversy exists relative to the treatment of the bone end. Aperiosteal technique has for years been advocated. By this is meant the removal of a cuff of periosteum about the periphery of the end of the bone. The cuff is variously recommended to be a quarter to one-half inch in width. This procedure does not seem a logical one as it deprives the underlying bone of a certain amount of blood supply. In the presence of any sepsis it will, in a high percentage of patients, result in a ring sequestrum. The procedure is therefore contraindicated in any secondary closure or secondary reamputation, or in any patient in whom there is any chance of an infected hematoma. Even in the absence of all infection, in some instances a ring sequestrum will form because of the avascular necrosis of the bone end, which has been deprived of periosteum.

The periosteum should be incised cleanly at the saw line and, at the completion of the bone section, the periosteum should be adherent to the end of the bone about its entire circumference. The only reason for the removal of any periosteum from the bone end is that the handling of this membrane has been faulty and rough, thus necessitating the removal of tags stripped loose.

Hemostasis is of utmost importance to the end-result of an amputation. Time should be spent tying all small muscle bleeders individually. The development of a moderate hematoma may delay recovery many weeks and even necessitate further surgery. To avoid the collection of blood, even after careful hemostasis, it is well to drain the stump with a small rubber drain for 48 hours. Many amputations are done under spinal anesthesia, and a reduced blood pressure may lead the surgeon to a false evaluation of hemostasis. It is well to know the patient's arterial tension before the wound is closed, and if it is 20 to 30 millimeters below his preoperative pressure, to have it raised to normal by an injection of ephedrine before the flaps are closed. This will often make what appeared a dry field bleed profusely.

No point in surgical technique has caused as much debate as the method of treatment of the nerve end. This debate has undoubtedly

Fig. 6.

Fig. 6. Technique of below knee amputation; skin not lifted off fascia, tibia tapered with periosteum adherent to end; nerves cut high in fascial plane.

Fig. 7.

Fig. 7. Technique of below knee amputation, muscle coned out so that only fascia and skin remain to go over bone end.

Fig. 8.

Fig. 8. Technique of below knee amputation. Fascia closed over end, drain placed beneath fascia; excess skin is removed so that in actual closure, very little skin is separated from fascial layer.

Fig. 9.

Fig. 9. Technique of below knee amputation. Skin closed without redundancy. Drain in angle of skin closure.

resulted from the distressing sequela of "phantom limb." Many chemicals have been advocated for injection into the nerve to prevent neuromas. The time honored method of alcohol injection has had a long period of usage. British authorities have in recent years advocated the use of formalin as a neurotoxic injection. A Russian school has advocated the cauterization of the artery of the nerve proximal to its distal end. Duck bill closures have been described. More recently a method of burying the nerve end in the medullary canal of the bone was described (Figs. 6 to 9).

It is well established that there is no chemical which will prevent the end of the cut nerve from healing by neuroma formation. I am unable to comment on the Russian method of depriving the tip end of the nerve of blood supply, but believe it only places the neuroma more proximally. The recently advised method of burying the nerve ends in the medullary canal of the bone is open to great objection if the nerve crosses a joint in the stump as it could easily lead to a nerve put under traction in many motions of the extremity.

For the past 3 years in the Amputation Service at Percy Jones Hospital, none of these methods has been used. In fact, little or nothing has been done to the nerves in an amputation stump except to treat them with respect and to hide their ends. The nerve should not be forcefully stretched so that it can be cut off high and then allowed to retract so that it will return to its normal length; rather the nerve trunk should be dissected and cut off high so that the neuroma which will inevitably result in the natural healing of the nerve end is well recessed in muscle. If a large bleeding vessel is present in the nerve, this should be ligated.

PHANTOM LIMB SYNDROME

In 2,988 amputations there have occurred 15 neuromas, which required surgical removal, and these could probably have been avoided had the surgeon been a little more thorough in the original operation. The only indication for the surgical removal of a neuroma is a superficial location, which would cause it to be subjected to pressure thus producing pain. This pressure may come either from the prosthesis or as a result of the bare stump resting on or striking, a hard surface, and can be demonstrated by palpating and tapping the neuroma, which will produce a "shock-like" sensation. The removal of neuromas for the treatment of any phase of the "painful phantom limb syndrome" will result in failure.

In this group of 2,783 patients, 4 instances of "painful phantom limb syndrome" have

occurred. Undoubtedly more instances of this distressing complication will occur in this group of patients as the years go on. A certain degree of phantom limb sensation seems to be almost physiological and this fact should be appreciated.

Every individual with an amputation has a phantom limb. Rarely does an individual with an amputation have a "painful phantom limb." This phantom sensation has a fairly uniform life history. It is present as a complaint in the days immediately following amputation and is usually more severe when the amputation has resulted from crushing trauma or is accompanied by great suppuration.

As healing progresses and inflammation and induration recede the patient complains less of the phantom pain. He will tell you that he has the foot or hand, but that it does not bother him. After the phantom has lessened and the patient has learned to live with it, any surgical procedure on the stump will aggravate the phantom phenomenon temporarily. This fact is true even though the surgical procedure in no way involves the nerve end. In many instances a simple excision of a skin scar in this group of patients resulted in an exacerbation of phantom pains. As healing again ensued, the disagreeable aspect of the phantom subsided.

When the patient puts on a prosthesis and uses it successfully, the phantom phenomenon rapidly assumes a less prominent place in his scheme of life. In fact many patients will proffer the information that the phantom is a help to them. It gives them some inkling of where their foot or hand is and what position it is assuming. This is the ordinary history of the phantom phenomenon.

The rare individual with the abnormal persistent "painful phantom limb" must be distinguished from the common group, who have the normal residual. Although rare, this type of patient is not hard to distinguish. Many times the distinction can be made by the patient's scars. Too often such a patient presents scars of removal of neuromas and section of nerve trunks at various levels in the stump. At the base of the extremity the scar of a surgical attack on the sympathetic nervous system may be present. In addition to these scars he may also present the pigmented marks of the morphine needle. The cure of a truly painful phantom limb by any surgery is extremely dubious. Certainly there is no basis for excision of neuromas or peripheral nerve section in the treatment of this complication of amputation, and sympathetic interruption does not have any great number of successes to recommend it. Whether the newly advised operations attacking the cerebral cortex will prove of value is not known.

Probably the only successful treatment of this problem is its prevention. Unfortunately, this cannot always be done by the surgeon as it is impossible for him to control the environment of his patients. However, in the early management of an amputee he can use narcotics judiciously and take all surgical measures to reduce and shorten extensive suppuration and tissue necrosis. It is almost universal that the picture of painful phantom limb is associated with the use of morphine or alcohol and with the poor adjustment of an individual to his environment. No surgery devised to date offers a cure for these unfortunates.

The following case history is illustrative of the complex nature of these patients.

A paratrooper lost his right arm in combat. He was a wiry little individual who had a great record for valor. His arm was knocked off by an 88 millimeter shell, and a companion applied a tourniquet. Following this he continued in combat for the next few hours until he was wounded in the thigh.

On admission to a hospital in the United States he was cheerful, hard to keep track of, and was all over the building. He had no complaints about his arm. He always seemed to enjoy talking about combat and his personal exploits. His amputation stump was revised and he was fitted with an artificial limb, which he used with great dexterity despite a very short stump.

After using his prosthesis for about 6 weeks he announced that he was returning to duty with the paratroops. This was most unusual but it seemed that while on vacation from the hospital he had gone to a paratroop base, where he contacted some commanding officer who asked for his return to duty. While on this leave he had also made some jumps.

Two months after leaving the hospital for duty he returned complaining bitterly and constantly that the fingers of his hand were clenched in the palm and that the nails were cutting the flesh and burning like fire, he could not sleep and paced the floor; the

Fig. 10.

Fig. 10. Roentgenogram of tendoplastic thigh amputation. Patella has been removed and quadriceps tendon has been turned over the end of the femur. The periosteum was left adherent to the distal end of bone. No spur.

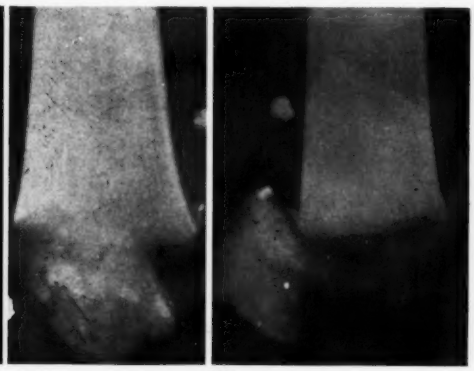


Fig. 11.

Foreign bodies were not removed.

Fig. 11. X-ray of Gritti-Stokes stump, in which patella has lost anchorage to femur and there is osteomyelitis of patella and femur.

typical picture of the "painful phantom limb syndrome."

On questioning this patient about the onset of the trouble he related the following story. After going to duty he did well and had no trouble. He had joined a paratroop battalion. After training with them he had finally talked his superior officers into sending him overseas again with the combatants. He arrived at the Port of Embarkation. Here he was given a medical examination. The examining medical officer put his hand on the prosthesis and, as he did so, said, "You can't go overseas with a wooden arm." The patient amputee said that at that instant he became infuriated, that the fingers of his amputated extremity dug into the palm of the absent hand with excruciating pain and that if his arm had been his own he would have slugged the damn doctor. This pain pattern had persisted since this disappointment.

This patient insisted his pains were due to palpable neuromas in the stump. At his insistence, and with great skepticism, these neuromas were removed. His complaints continued unabated. Then one day about 2 months after the removal of the neuromas, out of clear sky, he came to the Medical Officer in the ward with a telegram in his hand and announced that he was cured. He stated emphatically that he had no discomfort in his stump and no phantom sensation. To demonstrate his recovery he waved his prosthesis around and lifted a table off the floor with it. It had been impossible prior to this, to get the patient to wear the prosthesis. The telegram which he had received, was an order from a relief organization for him to go overseas for duty with them in the Zone of Activity.

This case history is well worth remembering. It does not infer that knowledge concerning the "painful phantom limb syndrome" is complete and that there may not come in the future some organic approach to this distressing problem. At present, however, the painful phantom limb syndrome should be listed as a condition not relieved by surgical treatment. A careful analysis of all these patients will reveal one or all of the following factors to play a prominent rôle, viz., drugs, alcohol, or severe maladjustment and frustration.

SKIN GRAFTS IN AMPUTATIONS

There has been some advocacy of the use of split skin grafts to hasten healing of open amputations and also of the use of pedicle grafts to conserve length in a short stump. No type of skin graft will stand the wear of a prosthesis and under no circumstances is even a pedicle graft a justifiable final procedure in the lower extremity. There may be rare instances in the upper extremity, in which a pedicle graft will preserve valuable length. In the arm the wear and tear from the prosthesis is not so great and the circulation of the stump is usually superior to the lower extremity.

Split grafts have been advocated to produce early healing of open amputations and shorten the time of invalidism. Split grafts can be successfully applied early to open amputation stumps. However, if these stumps are given the proper postoperative attention by keeping

Fig. 12.

Fig. 13.

a

Fig. 14. b

Fig. 12. Skin incision for Syme amputation.

Fig. 13. Disarticulating ankle from inside out in Syme amputation. The os calcis is being shelled out subperiosteally to prevent damage to blood supply of heel flap.

Fig. 14. Syme amputation. Section of tibia and fibula 1 centimeter proximal to articular surface of tibia. Section at this low level preserves flare of ankle joint. a, Saw in cut. b, Articular surface being removed.

traction applied, a split graft is not necessary. The use of split skin grafts to produce early healing does not make the final surgery for an open amputation easier but more difficult. The normal skin rather than coming over the end, as it does with traction, recedes to the margin of the skin graft. Consequently, when the final surgery is done there is a paucity of normal skin and the result is that useful bone length must be sacrificed. If a severely traumatized or burned extremity has extensive skin loss and there is much loss of plasma, early grafting may be the only means of restoring protein balance. Skin grafting of stumps for other than this reason is rather useless surgery. If for any reason skin grafts are to be used, the donor site should not be any place on the extremity which is expected to use a prosthesis, as too often painful, irritable keloids result at the donor site, which interfere with the wearing of a prosthesis.

END-BEARING STUMPS

There is considerable disagreement in opinion, regarding the ideal thigh stump. These differences of opinion are almost on the basis of nationalism. The British take the stand that no amputation stump is suitable for bearing weight on its end, and that end-bearing stumps will not stand up over a long period of time. They fit all lower limb prostheses, even for a below the knee amputation so that weight is borne on the ischial tuberosity.

The general consensus of American surgeons is that an end-bearing thigh stump is the best thigh stump possible. Certain Canadian surgeons are staunch advocates of end-bearing stumps and are great enthusiasts about the Gritti-Stokes thigh amputation, in which the patella is attached to the sectioned femur for the weight bearing end. They are also great champions of the Syme amputation, an end-bearing tibial stump. The British quite stalwartly condemn both the Gritti-Stokes and the Syme amputation.

Our experience makes us feel that an end-bearing thigh stump is the desirable type of thigh amputation to obtain when possible in an individual under forty. We have seen this type stump stand up under the most vigorous usage that can be given them, and we feel that the patient walks with a more secure and better gait. We are not greatly enthusiastic about the Gritti-Stokes type of end-bearing stump. The reason for this is that despite the best of technique in carrying out the operation, the patella will, in a certain number of instances, slide off the end of the femur, resulting in an unsatisfactory stump. Its scope of application is also very restricted. Where there is any chance of even the mildest sepsis, complications are likely to be very time consuming. It is an osteoplastic operation, which to be successful requires the patella to unite by bone to the end of the femur, just as any fracture heals. Even a mild infection may result in a failure of union of the patella to the femur, or in an osteomyelitis of both the patella and femur. Because of potentially infected tissue the Gritti-Stokes type of amputation is not often applicable to the re-

Fig. 15.

Fig. 16.

a

Fig. 17.

b

Fig. 18.

Fig. 15. Syme stump closed, drain in angle of incision for 72 hours.

Fig. 16. Syme amputation. Cruciate straps of sterile flannel glued to skin, immediately postoperative to prevent displacement of heel pad from center of stump.

Fig. 17. Good Syme stump. Weight bearing heel pad is centered under tibia, with neither varus nor valgus deviation. a, Anteroposterior view. b, Lateral view.

Fig. 18. Poor Syme stump. The heel pad has slipped to tibial side of stump.

amputation or closure of open amputations that have been done for trauma. In addition, the tendoplastic type of end-bearing thigh stump, in which the patella is removed and the quadriceps tendon turned over the end of the femur, produces an end-bearing thigh stump, which is just as good as the Gritti-Stokes stump (Figs. 10 and 11).

The Syme amputation has never been very popular in this country. It has had a lukewarm reception for the following reasons: Until the last few years it has been difficult to obtain a satisfactory prosthesis for this stump and American leg makers were not interested in supplying one. The Canadian limb makers have developed an excellent prosthesis for the Syme stump, which is now universally available in the United States. Being unfamiliar with this operation, American surgeons have had too many failures due to necrosis of the skin flaps and to a misalignment of the heel pad.

The operative technique and the postoperative care of this stump are more exacting than in any type of amputation. The blood supply of the heel flap comes almost completely from the medial side, through a branch of the posterior tibial artery. If the operation is done from the inside out, by disarticulating the ankle through the anterior portion of the incision and the os calcis is removed subperiostially, the blood supply to the heel flap is never endangered, and the chances of skin necrosis are obviated. If the foot is removed from the outside inward and the skin-fat flap of the heel is taken off the os calcis extra-

Fig. 19. Prosthesis on Syme stump (right leg). No corset above knee. The patient has below knee amputation of left leg which requires corset on thigh.

Fig. 20.

Fig. 20. Chopart foot stump. The anterior dorsiflexor muscle group have no attachment to tarsus. The remains of the foot is fixed in extreme equinus which is an unusable position.

a

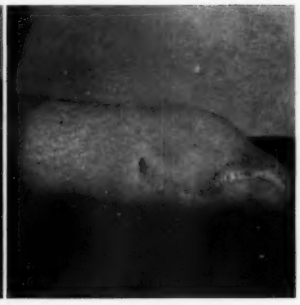


Fig. 21.

b

Fig. 21. Short below knee stump; projects 2 inches below thigh with knee flexed. Very valuable to patient in motivating prosthesis. Stump of this length should be saved. a, Anteroposterior view. b, Lateral view.

periostially, the blood supply of the flap will be cut off in a considerable number of instances.

There is a tendency for the heel flap to slide to the inside of the stump or to assume a varus position, so that the pad of the heel is to the end of the tibia, like a side car on a motorcycle, and this, of course, produces a useless stump. This sliding of the heel flap is very easily avoided by maintaining it in place over the end of the tibia with adhesive straps, which are changed at intervals for a period of 4 weeks. At the end of this time the pad is well stuck to the tibia and there is no further danger of medial displacement.

For a male the Syme amputation is the best possible amputation stump in the lower limb. It has the advantage that the prosthesis does not extend above the knee. In the prosthesis the patient can walk and stand longer than with any other type of leg amputation, and it is possible for a patient to walk with a gait that is so close to the normal that the public will not know he is an amputee. In addition to these facts, even without the prosthesis the patient need not use crutches or hop. Because of the length of the stump and because it is end-bearing, he can walk about the house at night, on the end of the stump, or when swimming or golfing he can get around to the shower and bath without having to carry crutches with him (Figs. 12 to 19).

The Syme amputation is not a good amputation for a woman. The prosthesis for this amputation is bulky and unsightly at the ankle. From a cosmetic viewpoint, it is probable that women would not be happy with this type of amputation, despite its superiority of function.

The British objection that this amputation will not stand wear and tear is without foundation. In Toronto there are many patients with a Syme stump, who have been at work on the stump every day during the 25 years which have elapsed between wars. We have also used this type of amputation in some 60 patients and they are doing well. It has been used whenever possible in all Army Amputation Centers during the present war and the American surgeon will become more acquainted with its value.

AMPUTATIONS THROUGH FOOT

Many types of amputation preserving the tarsal bones are described, among which is the Chopart amputation. These types of amputations are frequently tried because of the fact that they preserve the ankle joint. The Chopart amputation is doomed to failure and should not be done *if the muscles on the front of the leg have lost their attachment to the stump of the foot.* This is simple to determine. If these muscles have an attachment to the foot the patient can dorsiflex the foot stump. When the attachment of these muscles to the tarsus can be preserved the Chopart or any amputation through the foot should be done in preference to a higher amputation as the

a b c

Fig. 22. Arm amputation stumps of no functional value. a, Disarticulation of shoulder. b, Through surgical neck of humerus. c, At pectoral insection. (Courtesy *J. Bone Surg.*)

individual will be less handicapped. This, of course, does not apply to amputations done for arterial disease.

In instances where the anterior muscle attachments to the foot, the anterior tibial, cannot be preserved, the foot stump will gradually and inevitably assume a fixed equinus position due to the unopposed action of the gastrocnemius soleus muscle group, and the foot stump in this position will be a handicap rather than a benefit. In instances where this muscle imbalance cannot be prevented a Syme amputation is preferable to the deformed remains of the foot (Fig. 20).

SHORT BELOW-KNEE STUMP

A question which often faces the surgeon is how short a below the knee stump is useful and should be preserved. Or to put it another way, "How much of the leg must remain before an amputation is done through the femur and the knee discarded?" A good rule to follow is that any length of stump which can be seen to project when the knee is flexed should be saved. A stump which projects as little as 1 inch with the knee flexed is of value to the patient as a motor for moving the prosthesis through the normal knee. Although a patient with such an abbreviated below the knee stump will have to wear the same type of prosthesis as an above the knee amputee, he will use the prosthesis better and will have greater security and control in going down inclines. A patient with a stump which projects 2½ inches below the thigh when the knee is flexed will be able to do well with the ordinary below the knee prosthesis and will not need an ischial bearing prosthesis. An occasional leg maker will depreciate these short below the knee stumps, because they are difficult to fit, but the knee should never be sacrificed in an individual, who has good circulation, if the stump can be seen to project when the tibia is flexed to a right angle on the femur (Fig. 21).

UPPER EXTREMITY AMPUTATIONS

Amputations of the upper extremity are not common in civilian practice and it is therefore rare that a civilian surgeon has much experience in dealing with the problems of these individuals. The general attitude of surgeons toward amputations of the arm is

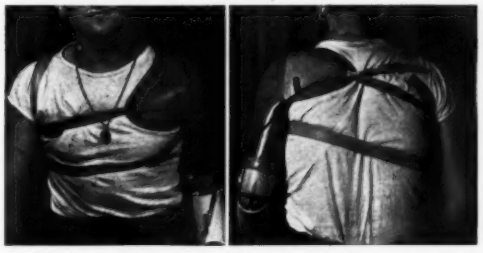


Fig. 23. Photograph of extensive harness required to keep prosthesis in place on amputation from pectoral insertion to shoulder. (Courtesy of *J. Bone Surg.*)

a

Fig. 24. b Fig. 25.

Fig. 24. a, Idea upper arm stump. b, Prosthesis on upper arm stump. Dotted area is space required for elbow block and mechanism. (Courtesy *J. Bone Surg.*)

Fig. 25. Prosthesis for an above elbow stump. Dark triangular area contains lock which patient must manipulate with other hand to obtain different degrees of flexion and extension. (Courtesy *J. Bone Surg.*)

"to save all possible." This is a good attitude but it can be elaborated a little further, as some arm stumps are more satisfactory than others.

No amputation through the humerus above the level of the humeral insertion of the pectoralis major produces a stump which has any functional value worthy of consideration. This fact does not mean that the head of the humerus should be removed unnecessarily, as it tends to round out the shoulder and from a cosmetic viewpoint is desirable. Even though an inch or two of the humerus remains, if the pectoral attachment has been lost, the end of the short piece of bone is pulled by the rotators into abduction and forward flexion. Amputations just below the pectoral attachment also produce stumps of little value in motivating a prosthesis. At this level the remainder of the humerus stays opposed to the thoracic wall and just a little forward and backward motion of the stump is possible; this movement is practically valueless in using an artificial arm. To maintain a prosthesis in place on these high amputations, an elaborate uncomfortable harness is necessary. Because of the uncomfortable harness, the weight of the prosthesis, and the uselessness of the artificial extremity, most patients ultimately discard the mechanical extremity and go about with an empty coat sleeve (Figs. 22 and 23).

The best site for an amputation through the humerus to secure the bone length adapted to the most efficient use of a prosthesis is the level just above the beginning of the flare of the condyles of the humerus. At this site 2 to 3 inches of bone above the elbow are removed. Amputation here is superior to a disarticulation through the elbow, as it allows room for the mechanism of the elbow block, without placing the elbow at a lower level than the remaining arm and thus making a disproportionate forearm. The absence of the condyles and the loss of the distal 2 to 3 inches of the humerus do not detract enough from the functional value of the humeral lever to offset the cosmetic and mechanical difficulties in the prosthesis (Fig. 24).

The importance of saving the elbow joint when possible cannot be too greatly stressed. The functional value of the elbow to the upper extremity is even greater than that of the knee to the lower extremity. Without an elbow joint under voluntary control, the arm amputee is limited to a few positions of the forearm, under the control of a mechanical lock, which he must unlock with the other hand to release. In close quarters, even with the ideal humeral stump, he may have to place the forearm of the prosthesis in one of a few positions available with the other hand. Even a relatively short stump of the forearm

will obviate this difficulty to a large degree. The short stump of the forearm need contain only a piece of the ulna, and the necessity for removing the proximal end of the radius does not interfere with active flexion of the elbow since the brachialis muscle attaches to the ulna. An elbow joint is of great value, even though it does not have total motion. A flail elbow joint is also of value. The condition of the humerus above the joint does not have to be normal to make the elbow worth saving. As the arm is not a weight bearing extremity, a fibrous union of the humerus may suffice for excellent use of the forearm stump, since the corset of the prosthesis will stabilize the humerus, as the sidebars will stabilize a flail joint at the elbow. No unnecessary reconstruction, which through long immobilization might lead to stiffness of the elbow should be proposed when it will jeopardize function (Figs. 25 and 26).

The ideal forearm stump is one through the junction of the middle and lower thirds of the forearm. This level provides enough bone length for a firm grip on the cuff of the prosthesis by the stump, and permits 2 to 3 inches of the volar surface of the forearm below the elbow to be unencumbered by the prosthesis cuff. This eliminates interference with flexion of the elbow caused by the cuff pinching and impinging on the front of the arm. This level is also just above the site at which the forearm becomes largely tendinous and avascular. Such a stump has an excellent blood supply, is warm, and will tolerate well the rubbing of a prosthesis cuff. Forearm stumps shorter than this are very useful, but, as the distance between the end of the stump and the insertion of the biceps decreases, the necessity for covering a greater proportion of the volar surface is increased, and flexion of the elbow may be interfered with by the encasement of the prosthesis. In the lower third of the forearm, after the muscles have merged with their tendons, there is poor circulation, as only main arteries traverse this area. Stumps through this area are cold and often cyanotic. Ulceration of skin is not uncommon in stumps in the lower third. The difference in temperature at these two levels can be easily detected by palpation with the hand.

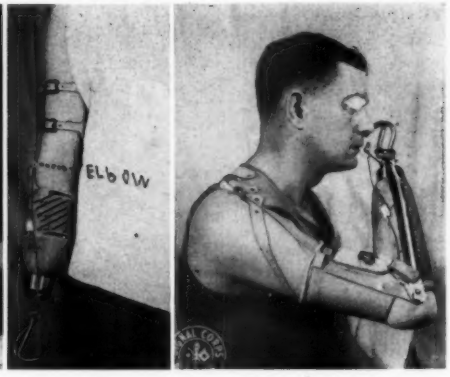
Fig. 26. a, left, Short, one bone (ulna) below elbow stump. b, Effective motivation of prosthesis by short below elbow stump.

Disarticulation through the wrist joint is not a good amputation. It has all the disadvantages of a stump in the lower third of the forearm. In addition, the inferior radioulnar joint may be very painful on pronation and supination. The loss of its carpal attachments and abutments causes a loss of stability of this joint which produces pain. The prominent subcutaneous styloid processes are prone to become abraded in the prosthesis, and the stump end is likely to be sensitive.

The stump which contains the proximal or proximal and distal rows of carpal bones is, however, a very useful and satisfactory stump from the functional viewpoint. From the cosmetic aspect, it has a few disadvantages. The reasons for the superiority of this stump to the disarticulation through the wrist are obvious. First of all, it must of necessity be covered by tissue with a good blood supply,—as the palmar flap of the heel and upper half of the hand. Second, the inferior radioulnar joint is stable and painless, because of the presence of its normal abutments and ligamentous support. Third, there are no bony unpadded prominences. The length of the stump containing carpal bones, together with the slight voluntary flexibility of this distal end, make it of considerable aid to the patient without a prosthesis. This stump can be used satisfactorily for a stabilizer in such activities as driving a car, tying shoe laces, tying a necktie, buttoning a coat, et cetera. This stump also requires much less harness to keep the prosthesis in place and to motivate it powerfully (Figs. 27 to 32).

a b

Fig. 27. a, Ideal forearm stump, at the junction of the lower and middle third. b, Roentgenogram which illustrates the ideal type of forearm stump. (Courtesy *J. Bone Surg.*)



a b

Fig. 28. a, Prosthesis on ideal forearm stump, showing space occupied by corset (cross-hatched area). b, Prosthesis in flexion, corset does not impinge on anticubital space. (Courtesy *J. Bone Surg.*)

The disadvantage of an amputation at the carpal level is largely in the fitting of a functional prosthesis. Because of its length, the mechanical hand or hook must hang at a lower level than the remaining good hand, since the necessary mechanism takes up space. This stump, however, lends itself well to the application of a purely cosmetic type of restoration,—such as those made of latex and plastics.

CINEPLASTIC AMPUTATIONS

The operation of cineplasty has received some publicity. Cinematization, or the making of skin tunnels in individual muscle groups of an arm amputation stump to move parts of a mechanical hand, individually, *must be regarded as a gadget.* Experience with this procedure following World War I was unsatisfactory and many of the individuals who had motor tunnels made after the War of 1914-1918 later had them removed. It is probable that the operation of cineplasty does have a very limited application for individuals doing certain types of specialized work, and that it may have a limited application in bilateral amputations of the upper arm. It is a

Fig. 29. a Fig. 30. b

Fig. 29. Roentgenogram of disarticulation through wrist. This is poor stump, due to circulatory deficiency, thin skin, bony prominences and unstable inferior radioulnar joint. (Courtesy *J. Bone Surg.*)

Fig. 30. a, Photograph. b, Roentgenogram. Amputation stump containing proximal row carpal bones and covered by palmar skin. Excellent stump. (Courtesy *J. Bone Surg.*)

simple surgical procedure that is not mutilating and it would seem that in certain well selected patients its trial might be justifiable. The skin tunnels can be easily removed without detracting in any way from the previous value of the stump, if they are found unsatisfactory.

PHYSICAL THERAPY IN POSTOPERATIVE CARE

Physical therapy has a definite rôle in the postoperative treatment of the patient who has lost part of an extremity, and this rôle is too often not clearly enough understood by the surgeon. Massage has very little place in returning the stump to its optimum condition. Its only use is to free an adherent scar. Its efficacy in shrinking a stump is of little value and is far surpassed by the use of elastic bandages, properly applied, and by the use of a temporary walking prosthesis, such as a pylon. The real shrinkage of the stump takes place with activity and weight bearing and may be so rapid as to make a new leg a poor fit in a few weeks. Shrinkage should be accounted for to a large degree before the permanent prosthesis is obtained.

The real value of physical medicine in the care of the amputee is in: (1) the prevention and relief of contractures and (2) the development of the muscles which will later be used in motivating the prosthesis.

It is a very common thing for an amputee to develop a contracture of a joint in the involved extremity, during the preoperative and immediate postoperative period. The joints most commonly involved in the lower extremity are the hip and the knee, and in the upper extremity the shoulder.

The flexion contracture of the hip is the most serious detriment to the proper use of a

Fig. 31. Prosthesis for forearm stump with carpal bones. a, left, Light harness. b, Powerful control split hook in any position. (Courtesy *J. Bone Surg.*)

prosthesis and is most frequently overlooked. This contracture is due to a shortening of the lateral or abductor muscles of the thigh. With the stump abducted it is not obvious; with the stump adducted it may be very prominent. This deformity makes it necessary for the patient in standing either to bend forward and thus succumb to gravity or to arch his back to compensate for the flexion, in order that he may have his head over his feet. The compensation by increasing the lordosis leads to backache and to early arthritic changes in the spine.

The fitting of a prosthesis to an abducted or flexed stump is difficult and the deformity must be compensated for. It is this deformity in the thigh stump, which leads to the bucket striking the adductors and pubis and causing great discomfort. In very short thigh stumps the flexion-abduction contracture cannot be obviated and the bucket must be especially constructed to accommodate for it.

In all thigh stumps which preserve half the length of the leg, this contracture can be re-

Fig. 32. Cosmetic latex hand on long carpal bone stump. a, left, Caucasian, cosmetic prosthesis on right hand. b, Negro, cosmetic prosthesis on left hand. (Courtesy *J. Bone Surg.*)

lieved by stretching exercises and the development of muscles which prevent it. The development of these contractures can also be obviated by the simple expedient of having the patient lie periodically on the stomach instead of sitting in bed with the hip flexed or propped up on pillows for 24 hours a day.

Flexion contractures of the knee occur frequently in below the knee amputations, and when present to over 10 degrees are a serious impediment to walking, as the partially flexed knee lets the patient down. They are best prevented and this is easily done by having the patient contract the patella, straightening the knee, which also helps to prevent atrophy of the quadriceps muscle. When present they usually yield readily to passive stretching of the hamstring muscles and the capsular structures.

In the upper extremity, the frozen shoulder, with the humerus bound to the side, is easily prevented by keeping the amputated extremity on an aeroplane splint in 90 degrees of abduction. This is also a very great adjuvant to healing as it obviates the dependent edema and bogginess in the tissues. A contracture of the shoulder will yield just as any adhesive bursitis to passive stretching of the contracted pectoral muscle and active exercise of the deltoid and rotators. No amputated extremity can be expected to use a prosthesis efficiently until all contractures are released.

The efficient use of an artificial leg in an above the knee amputee depends on the full development of the gluteus maximus muscle, which extends the hip and the adductor muscles which pull the leg toward the midline. Too often after the invalidism which has accompanied the surgery these muscles are atrophied and weak. Special exercises against resistance to strengthen these muscle groups should be instituted as soon as the stump is healed from surgery. It does not take a masseuse to carry these out and the surgeon who removes the leg should instruct the patient in them and see that he carries them out to the point of good muscular development, otherwise he has completed his job no more than has the surgeon who removes an eye and leaves an unsuitable socket for the artificial eye.

The patient with a below the knee stump, in addition to having good musculature to extend and adduct the hip must have good muscles to extend the knee. Exercises to develop the quadriceps femoris should be started early and continued until there is good strength in this muscle group.

The arm amputee must have a good deltoid, and if he has an elbow joint must have a good biceps to flex the prosthesis.

SUMMARY

1. The open circular or guillotine amputation is the safest type of procedure in the presence of infection. Proper after-care consisting of skin traction is a requisite to a good result in this type operation. A late secondary operation is necessary as a final procedure. This combination results in a better tailored stump than the open flap type of operation.

2. Fascia and skin or skin alone should be the only covering of an amputation stump. No muscle should be turned over the end of the stump. Aperiosteal technique is neither necessary nor sound. The nerve end should be well recessed under muscle. No chemical treatment of the nerve end is necessary. Complete hemostasis is necessary to good result.

3. Phantom limb is commonplace after amputation. "Painful phantom limb syndrome" is another thing. Drugs, alcohol, and psychic factors play a great part in the production of the latter. Surgical removal of neuromas does not benefit the established "painful phantom limb syndrome," and any surgical attack on the syndrome will in almost all instances result not only in failure to cure, but aggravation of symptoms.

4. Pedicle grafts are not satisfactory for weight-bearing stumps and will not stand the wear of a prosthesis. Skin grafting of open amputations is not necessary if proper after-care, consisting of traction, is carried out. Skin grafting does not facilitate final surgery.

5. End-bearing stumps are desirable in individuals under 40 years. They will stand up over time. The tendoplastic thigh stump is the best end-bearing thigh stump. The Syme amputation is the best possible stump in the lower extremity, if the foot must be sacrificed.

6. A below the knee stump which projects as little as 1 inch when the knee is flexed should be saved. It is of great help in motivating a prosthesis.

7. Any partial foot stump which has the anterior muscle groups attached should be saved. If the anterior muscle group is not attached a partial foot stump will inevitably go into severe equinus deformity and a Syme amputation is superior.

8. A humeral stump at or above insertion of the pectoralis major has no functional value. Every effort should be made to save the elbow joint even though the stump below it is very short. Long stumps with the carpal bones in are excellent. Disarticulation through the wrist leaves a poor stump. The best site for forearm amputation is the junction of middle and lower third.

9. Indications for cineplasty are extremely restricted. It should not be considered except in bilateral upper extremity amputees.

10. Physical therapy has a definite place in the preoperative and postoperative care of amputees. Massage is of very little value. The function of physical therapy is to prevent and release joint contractures, and to develop musculature.

CANCER OF THE CERVIX

A New Technique for Interstitial Implantation of Radium into the Parametrium

E. EUGENE COVINGTON, M.D., Baltimore, Maryland

A NEW technique has been developed for interstitial implantation of radium into the parametrium and lymph nodes of the pelvis in cancer of the cervix. This is a preliminary report on the first 100 cases. It is not an analysis of 5 year results as some of the patients have been treated less than 5 years. The patients treated so far have all been clinical stages I (3 cases), II (17 cases), and III (80 cases). Interstitial therapy is not justified in stage IV cancer of the cervix.

REASONS FOR A NEW TYPE OF RADIOTHERAPY

The new technique was developed for several reasons, chief of which are as follows:

1. *Inverse square law.* The inability to deliver enough irradiation into the parametrium and lymph nodes of the pelvis by the usual course of roentgen therapy combined with contracervical and intrauterine applications of radium. It should be emphasized that the loss of irradiation due to the inverse square law makes it impossible to concentrate a lethal (10 to 12 erythemas) dose of irradiation into the parametrium and lymph nodes along the lateral wall of the pelvis by the usual contracervical and intrauterine applications of radium. For example, if the true pelvis measures 12 centimeters in its transverse diameter the center of the pelvis (intrauterine canal) is 6 centimeters from the lateral wall. Due to the inverse square law it would take 36 times as much radium (3600 mgm. hrs. of radium) in the cervix to get 100 milligram hours of radium into the lymph nodes along the lateral wall of the pelvis. This amount would be 1 erythema or about one-tenth the amount of irradiation necessary to destroy cancer cells present in the lymph nodes along the lateral wall of the pelvis. It is thus obvious that some form of interstitial therapy is necessary to concentrate a lethal dose of radium into the parametrium and lymph nodes along the lateral wall of the pelvis.

2. *Local recurrences in the cervix.* There have been too many recurrences locally in the cervix and adjacent parametria following the usual amount of irradiation. In numerous clinics an average course of irradiation therapy is about as follows: 2000 r to each of four pelvic fields, followed by one application of contracervical and intrauterine radium (3000 to 4500 mgm. hrs. of radium). The author has seen too many positive biopsies after this form of therapy. A two dose technique of radium application, the last being interstitial, is now advocated; thus a greater amount of irradiation can be delivered to the cervix and a much greater amount to the parametria and lymph nodes of the pelvis. Pathologists have observed from autopsy studies a high percentage of deaths from cancer of the cervix with the tumor still localized to the pelvis and no evidence of generalized metastases. About one-third (reports of clinics vary from 20 to 35 per cent) of all deaths from cancer of the cervix are due to urinary obstruction from extension of the tumor into the parametria. Morton noted that almost 50 per cent of the cases of cancer of the cervix had microscopic cancer cells present in the cervix at the time of operation. This high percentage of residual cancer after radium treatment is not general throughout the country, but it does strengthen the argument that there are still too many cases in which the cancer, still localized to the cervix, has not been eradicated by radium. Taussig and Meigs have found positive glands in the pelvic lymph nodes at operation in

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almost one-third of all early cases (stages I and II) when they were not suspected clinically before operation. Many observers, Teahan, Pomeroy, Pitts and Waterman, and Arneson, dissatisfied with their results in cancer of the cervix with parametrial extension, are advocates of interstitial implantation of radium element needles or radon seeds into the parametrium through the vaginal route. It is thus obvious that interstitial therapy is necessary and must accomplish two purposes; a higher total dose of irradiation to the cervix, and a more equal distribution throughout the parametria and lymph nodes of the pelvis of a lethal dose of irradiation.

3. *Trend back to surgery.* Within recent years there has been a renewed interest in the Wertheim type of panhysterectomy, usually associated with the Taussig type of lymph node dissection, for selected cases of early (stages I and II) cancer of the cervix. Many gynecologists now believe the combination of irradiation followed by panhysterectomy will give a higher percentage of 5 year cures than either procedure alone. It is certainly true that a panhysterectomy is a much safer surgical procedure after the gross tumor has been almost entirely destroyed and the secondary infection cleared up by previous irradiation therapy.

Surgeons have three good reasons for their belief in a radical type of panhysterectomy for cancer of the cervix: (1) There are still a few cases in which the cancer of the cervix cannot be controlled by the present-day type of irradiation. (2) About one-third (Taussig, 33⅓ per cent, and Meigs, 17 per cent) of all early cases (stages I and II) will have cancer cells in the pelvic lymph nodes at operation. Irradiation has a delaying effect on such cancers, but a low 5 year cure rate. (3) Improvements in surgical technique, especially the modern advances in the control of infections, have so lowered the operative mortality and morbidity that panhysterectomy is a safer procedure than in former years. Panhysterectomy then should offer a better 5 year cure rate in early cases, and it is now up to the radiologists to offer something equal to this definite step forward obviating the necessity of resorting to major surgery.

TECHNIQUE OF RADIOTHERAPY

The author advocates a new technique for delivering a greater dose of irradiation to the cervix and a much greater dose equally distributed throughout the parametria and lymph nodes along the lateral wall of the pelvis.

First radium treatment. As the first treatment 3600 milligram hours of radium, with 1 millimeter platinum as a filter, was used as follows: One long rubber tandem (90 mgm. of radium × 24 hrs. = 2160 mgm. hrs. of radium) was inserted into the intrauterine canal and a rubber tandem (30 mgm. of radium × 24 hrs. = 720 mgm. hrs. of radium) was packed with gauze as far laterally as possible into either lateral vaginal fornix. This procedure gave a fairly equal distribution of irradiation throughout the pelvis. A serious mistake, and probably the most common cause of radiation necrosis, is to concentrate a large quantity of radium in a small area, usually the contracervical region, giving an overdosage and thus necrosis in that small area and not enough throughout the pelvis. Packing the rubber tandems in the vaginal fornices with gauze is better than colpostat technique. There are so many anatomical variations and variations in the amount of cancer present that in many instances the colpostat technique was impractical. Five grams of sulfanilamide was routinely dusted on the cervix before the gauze packing. In the present day of sulfonamides and penicillin to control infections there is no reason to use roentgen therapy first for this purpose.

Roentgen therapy. Within a few days (usually 1 to 7) after the first radium treatment roentgen therapy was started, which was as follows: 2000 to 2400 r was given to each of four pelvic fields over a period of 4 weeks. The physical factors were: 400 kilovolts, Thoreus filter (1.75 mm. sn., .8 mm. cu., and 1 mm. al.), 50 centimeters distance, and 15 centimeter cone portals. This technique gave a 42 per cent depth dose (42 per cent of 8000 r = 3360 r in the tumor) into the cervix (10 cm. depth) and adjacent parametria.

New interstitial radium technique. As soon as the roentgen therapy was completed (usually 30 to 35 days after the first radium

treatment) the second treatment or interstitial implantation of radium was done. By this time the secondary infection was usually cleared up and most of the gross tumor, especially the friable type of cauliflower growth, was almost entirely gone. A search of the literature reveals that no one has used exactly the same interstitial technique of radium as will now be described in detail as the author's technique: Four small incisions (.5 cm.) were made in the vaginal mucosa at equidistant points as far laterally from the cervix (usually 2 to 3 cm.) as possible. The incisions were actually in the 2, 4, 8, and 10 o'clock positions around the cervix (Figs. 1, 2, and 3). It should be emphasized that the cutting was only through the vaginal mucosa and not into the parametria. A long Kelly clamp was next used to dissect a long tract (usually 2 to 4 cm.) into the parametrium through each of the four incisions. This dissection is the most dangerous part of the whole procedure; but by care, patience, and experience the author has now done this new procedure in well over 100 patients with no evidence of injury at operation to a blood vessel, ureter, bladder, or rectum in a single case.[1] After dissection of the four tracts as described, four rubber tandems were made up as follows: two tandems contained 25 milligrams of radium, and two tandems contained 20 milligrams of radium (usually 2 tubes of 10 mgm. each). A rubber tandem was then inserted into each of the four tracts. This gave 1260 milligram hours of radium (45 mgm. of radium × 28 hrs. = 1260 mgm. hrs. of radium) into either parametrium or a total of 2520 milligram hours of interstitial radium. A long rubber tandem (60 mgm. of radium × 28 hrs. = 1680 mgm. hrs. of radium) was then inserted into the intrauterine canal. Five grams of sulfanilamide was routinely used locally and the vagina was packed with gauze. The gauze packing helps to push the bladder and rectum forward and backward respectively away from the radium.

TABLE I.—TOTAL IRRADIATION GIVEN IN 100 CASES

	Radium dosage mgm. hrs.	mgm. hrs.	Roentgen dosage r
First radium in intrauterine canal	2160		
Second radium in intrauterine canal	1680		
Total in intrauterine canal		3840	
First radium in right fornix	720		
Second radium in right parametrium	1260		
Total in right fornix and parametrium		1980	
First radium in left fornix	720		
Second radium in left parametrium	1260		
Total in left fornix and parametrium		1980	
Total radium		7800	
Roentgen therapy in cervix and parametria (8000 r given, depth dose equals 42 per cent at 10 cm. with 400 kv.)			3360

TOTAL RADIATION GIVEN

A glance now at Table I will show that irradiation given over a period of 35 to 40 days, by use of a two dose radium technique, the last being an interstitial application, combined with roentgen therapy as described accomplished two purposes; a high total dose given to the cervix (3840 mgm. hrs. of radium + 3360 r—42 per cent of 8000 r—of roentgen therapy), and a high total dose fairly evenly distributed throughout the parametria and lymph nodes of the pelvis (1980 mgm. hrs. of radium + 3360 r of roentgen therapy to either parametrium). The total irradiation given directly into the tumor is thus 7800 milligram hours of radium + 3360 r of roentgen therapy.

CONTRAINDICATIONS FOR INTERSTITIAL RADIUM THERAPY

Interstitial implantation of radium was always discontinued for any of the following three conditions:

1. *Radiation fibrosis.* There was an occasional patient, most commonly an elderly woman, who would develop so much fibrosis from the first radium treatment and the 8000 r of roentgen therapy previously given, that the

[1] This new dissection and implantation of radium technique was done several times in the autopsy room on fresh cadavers before attempting it on patients. The dissection of the 4 tracts was done in the manner described and dummy radium tandems were implanted. The abdomen was opened and the locations of the 4 tandems were studied in their anatomical relations to the ureters, big blood vessels, bladder, rectum, and peritoneum, and their distances from the cervix and lateral wall of the pelvis were measured. The tandems were usually 2 to 3 centimeters lateral to the cervix, medial to the big blood vessels, and lateral to the ureters.

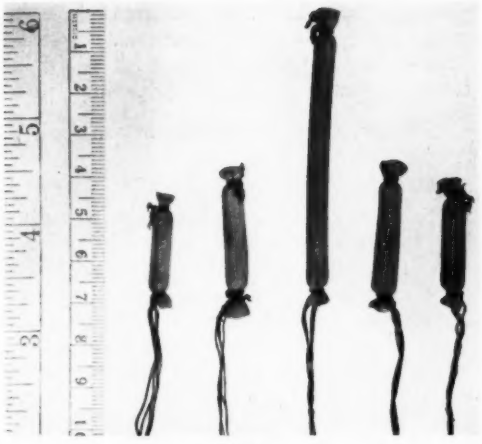

Fig. 1.

Fig. 1. Photograph of the actual radium tandems used for this series of 100 cases. There are 4 rubber tandems (2 contain a 25 mgm. tube of radium and 2 contain a 20 mgm. or 2 10 mgm. tubes of radium) for interstitial implantation into the 4 carefully dissected tracts of the parametria and a long rubber tandem (either 3 20 mgm. tubes or 2 30 mgm. tubes of radium) for intrauterine application. The tandems are made of Dakin's tubes (2 mm. of rubber) with strong silk strings attached. The filter is thus 1 millimeter platinum, 2 millimeter rubber. It will cause less necrosis than radon seeds (.3 mm. gold filter).

Fig. 2. Artist's drawing of implantation. Note the positions of the 4 tandems for interstitial implantation situated at equidistant points (2 to 3 cm. lateral to the cervix) at 2, 4, 8, and 10 o'clock positions. Note the absence of a contracervical application. The author believes they concentrate too large a dose of irradiation to the cervix and thus cause necrosis.

Fig. 3. Photograph of a roentgenogram showing the locations of tandems and the long intrauterine tandem (the 2 large radium capsules centrally located). Note that the 2 tandems in either parametrium are about one-half the distance from the middle of the pelvis (intrauterine canal) to its lateral wall, thus giving a wide and equal distribution of a lethal dose (1260 mgm. hrs. of radium) to either parametrium.

Fig. 2.

Fig. 3.

dissection was difficult and probably too dangerous. Interstitial therapy would surely cause more fibrosis and thus increase the possibility of late complications, i.e., urinary obstruction from stricture of the ureters, sciatic nerve pain from the pressure of scar tissue on the sciatic nerve plexus, or stricture of the rectum.

2. *Infection.* An occasional patient, usually with the infiltrative type of lesion, still had too much infection present following the

previous radiotherapy to justify the risk of dissection and parametrial implantation of radium. A persistence of infection was nearly always due to two causes: (1) radiation necrosis from a previous overdosage of radium concentrated to a small area, or (2) uncontrolled cancer. A combination of local infection and radiation necrosis was usually a sign of a bad prognosis.

3. *Advanced cancer.* Many times examination under anesthesia would reveal a more advanced lesion than was thought present before operation. This has been a common error. Many of the cases, especially in the early days of development of the new technique, called stage III we would now classify as stage IV. The personal equation and enthusiasm of different authors vary and thus the differences noted in the classifications of the clinical stages of cervical cancer.

ADVANTAGES OF INTERSTITIAL RADIUM THERAPY

The author claims the new technique of interstitial radium implantation into the parametria has the following advantages: (1) It eliminates the necessity for an abdominal operation. (2) Positive biopsies after treatment are less than was noticed by the older method of therapy, thus the 5 year cure rate should be higher. (3) It gives a more equal distribution and higher total dosage of irradiation in the parametria and lymph nodes of the pelvis. There have been only 4 cases (4 per cent) of death from urinary obstruction due to parametrial extension as contrasted with the 20 to 35 per cent as recorded in the literature. (4) The filter (1 mm. pt. + 2 mm. of rubber) causes less necrosis than radium needles or radon seeds. Radon seeds have a filter of .3 millimeter of gold, which allows enough beta rays to pass through to cause necrosis adjacent to the seeds. (5) There is no danger of puncturing a blood vessel, ureter, or bladder when the blunt rubber tandems are inserted into the four carefully dissected tracts. This is a serious danger when radium element needles or radon seeds are inserted blindly into the parametrium. (6) Radium element needles with silk strings attached will occasionally get hung in the tissues on attempted removal. Several observers have had this embarrassing experience, making operative removal necessary. This mishap has not occurred with the rubber tandems placed in the carefully dissected tracts.

COMPLICATIONS OF INTERSTITIAL RADIUM THERAPY

The possible complications of this new technique for interstitial implantation of radium into the parametria were both early and late.

Early complications. The dangers or possible early complications from the operation were as follows: (1) damage to the ureters with extravasation of urine, (2) damage to a large blood vessel with hemorrhage, (3) opening the peritoneal cavity with peritonitis as a result, and (4) pelvic cellulitis through any one of the four openings into the parametria. In this first 100 patients treated by the new technique none of these possible mishaps have occurred. This fact alone convinces the author that the new technique is certainly a safe procedure and could be learned easily by any radiotherapist with surgical training. Cystitis, proctitis, irradiation sickness, and erythema with desquamation of the skin around the pelvis were noted with about the same frequency with the new technique as was noted by older methods. They were at times troublesome and annoying to the patient but never serious.

Late complications. The late complications from interstitial radium implantation were more serious than the early and were noted as follows: (1) A fairly severe proctitis was the most common late complication and was noted in 6 patients, 1 of whom developed a stricture severe enough to require colostomy. The other 5 patients still have occasional attacks of diarrhea with bloody mucus in the stools. Proctoscopic examination showed the typical picture of irradiation proctitis, usually most pronounced about 6 to 8 centimeters above the anus. All 6 of these patients are clinically free of cancer. (2) Rectovaginal fistulas have been produced in 4 patients, 3 of whom probably had stage IV cancer and should not have been treated by interstitial therapy. All 3 of these patients have necroses, fistulas, and still have positive biopsies after the heavy total dose of irradiation given in this series. The fourth patient is living and clinically free of

cancer over 5 years, but she still has the fistula. The author considers this fistula was due to overirradiation. (3) Irradiation necrosis of the cervix was present in several cases, especially the late stage III (or IV?) cases, in most of which cancer was still present locally in the cervix after treatment. One patient has developed late irradiation necrosis of the cervix several months after treatment and is still clinically free of cancer. (4) Urinary obstruction was the ultimate outcome in 4 patients, each of whom had cancer clinically in the parametrium, and in 2 cancer was proved by autopsy. This complication was studied carefully because interstitial radium therapy always produces more fibrosis than external irradiation. It is certainly safe to say that extension of cancer into the parametrium was several times more common as the cause of obstruction to the ureters than irradiation fibrosis. (5) Secondary vaginal hemorrhages were a serious complication in 7 cases. There was also 1 fatality from rectal hemorrhage. In every case of secondary hemorrhage the patient had uncontrolled cancer in the cervix.

Briefly to summarize the complications of interstitial irradiation, there were no early complications from the implantation; but there were 6 cases of irradiation proctitis, 1 case of rectovaginal fistula, and 1 case of radiation necrosis of the cervix as late complications. All the remaining cases of fistulas, necroses, secondary hemorrhages, urinary obstructions, and distant metastases were due to uncontrolled cancer and not to overirradiation.

RESULTS

The primary purpose of this paper was to show the necessity of interstitial radium therapy for cancer of the cervix and the advantages of a new technique used by the author in 100 cases. It is not a 5 year study as a few of the patients were cared for less than 5 years ago. Seventy-six patients (76 per cent) are still living and under observation and 24 patients (24 per cent) have died of cancer. The known causes of death were as follows: 3 patients had rectovaginal fistulas, 2 had bone metastases, 2 had pulmonary metastases, 4 died of urinary obstruction, 7 had secondary vaginal hemorrhages, and 1 died of rectal hemorrhage.

SUMMARY AND CONCLUSIONS

From a study of the 5 late complications of irradiation, the causes of death in 24 patients, and the high percentage of positive biopsies of lymph nodes of the pelvis found at operation by surgeons, it should now be obvious that a higher total dose of irradiation should be given to the cervix and a much higher total dose equally distributed throughout the parametria and lymph nodes of the pelvis.

1. There were no early complications from the interstitial implantation of radium, but there were 6 cases of irradiation proctitis, 1 case of rectovaginal fistula, and 1 case of radiation necrosis of the cervix as late complications. The 24 deaths were the result of uncontrolled cancer of the cervix and adjacent parametrium.

2. The advantages and contraindications of the new type of interstitial therapy were discussed in detail. Emphasis was placed on the greater safety of this procedure over other forms of interstitial therapy.

3. The author has tried to accomplish the following: (1) To eliminate the necessity of a major surgical procedure for early carcinoma of the cervix. (2) To improve the complete eradication of the growth in the cervix. There have been fewer positive biopsies after treatment, thus the 5 year cure rate should be better. There have been only 4 deaths (4 per cent) from stage II cancer of the cervix and none from stage I. This rate is far better than was obtained by previous methods of radiotherapy. (3) To reduce the number of deaths from parametrial extension of cancer by giving a higher total dose of irradiation equally distributed throughout the pelvis. This has also been effected as only 4 deaths (4 per cent) were due to urinary obstruction contrasted with the usual 20 to 35 per cent recorded in the literature.

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CORRECTION OF ESOPHAGEAL ATRESIA AND TRACHEO-ESOPHAGEAL FISTULA BY CLOSURE OF FISTULA AND OBLIQUE ANASTOMOSIS OF ESOPHAGEAL SEGMENTS

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MORE than 400 cases of congenital atresia of the esophagus, with and without tracheo-esophageal fistula, have been recorded in the literature. Prior to 1939, no therapeutic success had been obtained by any method of surgical treatment. Many of these babies have died because of other congenital abnormalities, but the majority have succumbed from complications directly arising from the esophageal malformations. The outstanding causes of death have been (1) pneumonia from spill-over of milk or saliva from a blind upper end of the esophagus, (2) pneumonitis from regurgitation of gastric juice through a lower esophageal segment and tracheo-esophageal fistula, and (3) starvation because of discontinuity of the esophageal tube. Obviously, the condition is incompatible with life unless surgical relief can be instituted. Numerous methods have been devised to prevent contamination of the lungs and to provide a method for feeding. In general, two successful approaches have been developed. In the first, the tracheo-esophageal fistula has been closed, the upper end of the esophagus has been marsupialized in the neck, and a gastrostomy has been established in multiple stage procedures, with the idea of constructing an anterior thoracic esophagus at a later time. Leven, Humphreys, and notably Ladd have been advocates of this therapeutic regimen. In the second, an attempt has been made to close the tracheo-esophageal fistula and simultaneously establish the continuity of the esophagus by direct anastomosis of its upper and lower segments. This latter method is only applicable when the distance between the esophageal ends is not too great.

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Several forms of direct anastomosis of the esophagus have been described for babies. Some of these have been followed by successful reconstruction of the esophagus and by survival of the patients. Such cases are those of Daniel, Haight(2,3), Humphreys, Ladd, and the one here recorded. As yet, there is insufficient experience to permit a final evaluation of each method of anastomosis which has been used. Hence, it is important in this early stage of such surgical endeavor to record the various ways in which esophageal repair has been accomplished, so that in the future we can select the one which appears to be the most promising. With this in mind, we are prompted to report the following case because the surgical technique which was employed seemed to contribute to a most favorable result which was obtained for the child.

It is not our purpose to present a complete treatise on the recognition, the roentgenologic appearances, and the classification of the congenital abnormalities of the esophagus, nor do we intend to summarize the surgical methods for construction of an artificial esophagus. Most aspects of these various problems have been adequately covered in the publications of Vogt, Lanman, Haight(3), Humphreys, Ladd, and others. These articles are recommended to the reader who might desire specific or detailed information along such lines.

CASE REPORT

R. J. T., a 2 day old male infant, was referred to the Children's Hospital on July 29, 1944 by Dr. Maurice Adelman of Providence, Rhode Island, because of regurgitation of feedings and recurrent cyanotic spells since birth.

The baby had been born at full term after an uncomplicated pregnancy and an easy, short labor. Birth weight was 6 pounds 12 ounces. Breathing was spontaneous and the cry was lusty. A few hours after birth it was noted that excessive accumulations

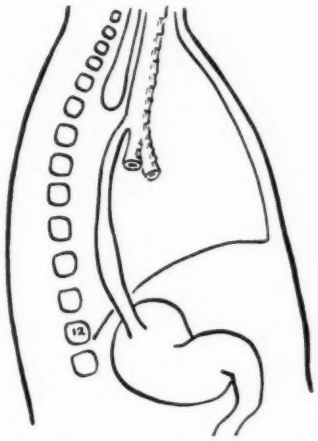

Fig. 1. Schematic representation of abnormality in case here reported. Upper end of the esophagus ends blindly. Lower end of esophagus communicates with posterior portion of lower part of the trachea. Superior segment of the esophagus is slightly dilated, while the inferior one is quite small.

of saliva appeared in the baby's mouth and it was necessary on several occasions to suck these away in order to establish a satisfactory airway. On the second day of life, a dilute formula was offered, but the feedings were promptly regurgitated. All attempts at feeding were followed by respiratory difficulty and cyanosis. The infant was seen in consultation by Dr. Adelman and was referred to this hospital with a diagnosis of esophageal atresia.

Physical examination on entry showed a well developed and well nourished white male infant in no acute distress. Temperature was 99.2 degrees F., respirations 24, pulse 120. The color was good and there was no cyanosis at the moment. The skin had a slightly icteric tint which was regarded as a physiological jaundice. The head, eyes, ears, nose, and throat were normal. The sides of the chest moved equally; there was no intercostal retraction. The percussion note was resonant over both lung fields. There were numerous fine, moist râles and coarse rhonchi throughout the entire chest, more marked at the right apex. The heart was not enlarged to percussion. The cardiac sounds were of good quality and the rhythm was regular. There was no murmur. The abdomen was slightly tympanitic, and was normal to palpation. The liver edge was felt just below the costal border. The genitalia, extremities, and reflexes were normal. By rectal examination, meconium was found on the examining finger.

Roentgenologic examination was made immediately after admission. Under the fluoroscope, a No. 8 French, urethral catheter was passed through the infant's nose and down into the esophagus. The catheter would not pass into the stomach since it met some obstruction in the middle portion of the esophagus. Two cubic centimeters of lipiodol were now introduced through the catheter. A blind esophageal pouch (atresia) was demonstrated at the level of the 4th thoracic vertebra (Fig. 2). Fluoroscopy and film studies showed a considerable amount of gas scattered through the stomach and intestines, indicating the existence of a fistula between the trachea and the lower segment of esophagus. There were patches of atelectasis and emphysema throughout both lung fields, the changes being most marked in the right upper lobe.

The infant was placed in an oxygen tent. The upper, blind end of the esophagus was kept cleared out by an inlying catheter which was passed in through the nose and was connected to a Wangensteen suction apparatus. Intramuscular penicillin was started in doses of 3,000 units every 3 hours. Sodium sulfadiazine was given subcutaneously, with an initial dose of 1½ grains, and subsequent doses of ½ grain every 4 hours. Parenteral fluids were administered; 70 cubic centimeters of 5 per cent glucose in water intravenously and 100 cubic centimeters of 2½ per cent glucose in 0.47 per cent saline hypodermically. After 12 hours of this therapy, the râles had largely disappeared from the chest and the infant's condition seemed optimal for operation.

Operation (by R.E.G.). Under cyclopropane anesthesia, given with a tightly fitting face mask,

Fig. 2. Lateral roentgenogram, with baby in upright position. A catheter has been introduced into upper portion of the esophagus and 2 cubic centimeters of lipiodol have been instilled. This iodized oil outlines lowermost extent of the blind upper sac. Air in the stomach and intestines indicates that the trachea must communicate with the lower esophageal segment.

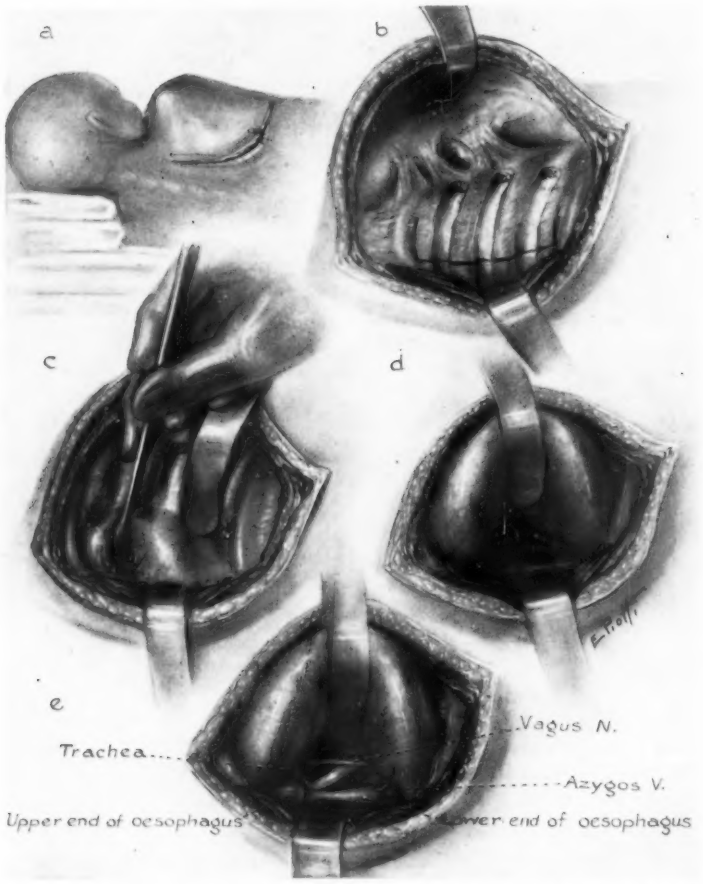

Fig. 3. Operative approach; after Lanman, Ladd, and Haight and Towsley. a, Curvilinear incision, dividing lower part of the trapezius muscle and the rhomboid major, so that the scapula can be retracted laterally. b, Scapula retracted. Portions of 3rd, 4th, and 5th ribs resected subperiosteally. Intercostal muscle bundles will be cut posteriorly along the black line. c, Peeling parietal pleura off at posterior chest wall and pushing it forward. d, Azygos vein coming into view in depths of wound. e, Azygos vein divided, entrance to mediastinum provided. Mediastinal structures exposed.

the infant was placed in a prone position with the right shoulder elevated slightly (Fig. 3). A curved incision was made just inside the medial border of the right scapula, running downward and outward around the angle of the scapula. The superficial muscles were divided and the scapula was reflected upward and laterally, and the costal cage exposed. The erector spinae muscles were mobilized slightly toward the midline. Subperiosteal resection of the segments (about 3 cm. long) of the 3rd, 4th, and 5th ribs was now carried out. The bundles of intercostal muscles with their accompanying nerves and vessels were divided. The pleura was then stripped forward by blunt dissection from the vertebral bodies, and the azygos vein exposed. This vein was doubly ligated and divided. Dissection was continued until the mediastinal structures were adequately exposed. The upper blind pouch of the esophagus extended down to a point opposite the lower portion of the trachea. The lower segment of esophagus had a fistulous communication with the posterior surface of the trachea about ⅛ inch above the carina (Fig. 4a). There was some thin areolar tissue between the two esophageal segments. The lower part of the

esophagus was now extensively mobilized as far down as the diaphragm, though this was accomplished at considerable risk to its blood supply. The tracheo-esophageal fistula was ligated with No. 0000 silk close to the trachea and was then divided (Fig. 4b). A long slit was cut in the lower esophageal tube. The upper esophageal pouch was extensively freed from surrounding structures up to the base of the neck. The thinnest area of this pouch was on its anterior surface, along which an opening was made. Stay sutures of No. 00000 silk were placed in the four quadrants of each esophageal end. The No. 8 urethral catheter in the nose and upper esophagus was now pushed downward by the anesthetist so that it could be threaded into the lower segment and into the stomach. The near ends of the stay sutures were first tied, following which the far ends were tied, and thus the walls of the esophagus were rolled inward at the anastomosis. Next, 7 or 8 interrupted sutures were used to join and turn in the muscularis between the stay sutures. An effort was made to establish an *oblique* type of union, in the belief that this might have less tendency to subsequent stricture formation. In anticipation of this type of junction, slits had been made in each segment, and it was thought desirable to make each slit where the respective segment seemed thinnest. In each case this was on the anterior surface. Unfortunately, this procedure necessitated rotating the lower segment through a twist of 180 degrees in order properly to appose its opened end to that of the upper pouch. (However, this twist has in no way interfered with the subsequent function of the esophagus). The mediastinum was thoroughly irrigated with saline, sucked out, and then filled with 25,000 units of penicillin solution. A narrow strip of soft rubber drain was placed near the anastomosis and was led out through the inferior angle of the skin wound. The chest was repaired by joining the intercostal muscle bundles posteriorly, closing the superficial muscle layers, and then approximating the skin. Deknatel No. 00000 silk on atraumatic needles was employed throughout the procedure, for both the esophageal anastomosis and the wound closure. The infant stood the operation quite well.

Postoperative course. The baby was again placed in an oxygen tent which was discontinued in 24 hours. Four hours after operation, breast milk was injected through the inlying gastric tube, and was increased in a few days to supply full caloric requirements. A transfusion was given after operation and on the following day. Clyses were continued for 4 days. The infant's pulse and general condition were extremely satisfactory throughout the postoperative period. The mediastinal drain was removed on the 5th day, there having been a discharge of only a few cubic centimeters of thin, serosanguineous fluid. The wound was solidly healed at the time of removal of sutures 3 days later.

Since we were unwilling to attempt feedings by mouth at so early a date, and since we did not care to leave the nasal tube in place for a longer period, a

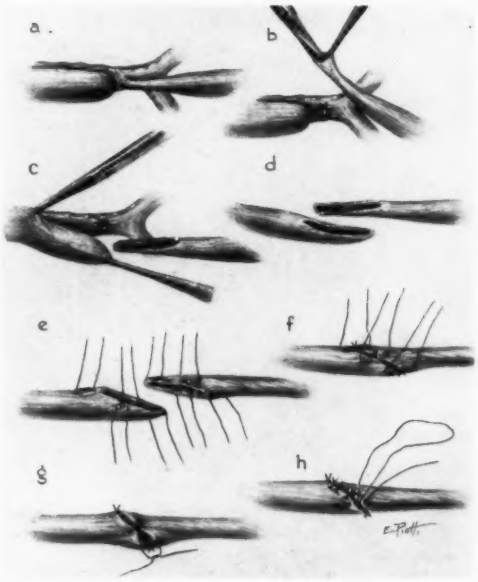

Fig. 4. Details of operative procedure. a, Blind upper esophageal pouch at left. Lower esophageal segment communicates by fistula with lower part of trachea. b, Fistula ligated. Lower segment mobilized and then slit open along its anterior surface. c, Upper segment being separated from trachea. d, Upper segment opened along its anterior surface. e, Four stay sutures in each segment. f, Proximal ends of stay sutures tied. g, Distal ends of stay sutures tied so that esophageal ends roll in. h, Completing oblique anastomosis with interrupted sutures.

Stamm gastrostomy was established under local novocain anesthesia on the 8th postoperative day. At this time the inlying nasal catheter was removed and gastrostomy feedings were started. Four days later breast milk feedings were begun orally with caution. Since small quantities of milk were swallowed without hesitation, the oral feedings were increased rapidly in amounts during the next few days. Because no difficulty was encountered in deglutition, the gastrostomy was allowed to close and the baby was discharged home on the 20th hospital day, weighing 7 pounds and taking full feedings by mouth. Sulfadiazine was used for 1 week after the mediastinal operation. Penicillin was continued for the whole period of hospitalization.

Since leaving the hospital, this baby has had a most satisfactory course. The feedings have been taken easily and with facility. The nursing bottle has usually been emptied in 12 to 15 minutes; rarely has it taken longer. The addition of cereals and vegetables to the diet has not resulted in dysphagia. At no time has there been any gurgling or wheezing after the act of feeding. Fluoroscopic examination on three occasions has shown that barium passed

Fig. 5. Photograph of back on 19th postoperative day. The wound healed without infection and without esophageal leakage.

Fig. 6. Photograph of patient at 6 months of age, showing excellent general status.

quickly through the esophagus. There has been some visible constriction at the site of anastomosis and the lumen of the esophagus above this level has been somewhat larger than the lumen below it. However, dilatations of the esophagus were not done at any time during the first year of life. The child's general physical condition has been excellent (Fig. 6) and the weight gain has been most pleasing (Fig. 7).

At about 1 year of age, the child began to have some difficulty with swallowing of solid food and was returned to the hospital for short periods in the 13th, 14th, and 15th months of life, at which time the esophagus was dilated respectively to No. 30 (French), No. 30, and No. 41. Following this last and more thorough stretching, deglutition has been very satisfactory. When last seen at 20 months of age there was no hesitation in swallowing.

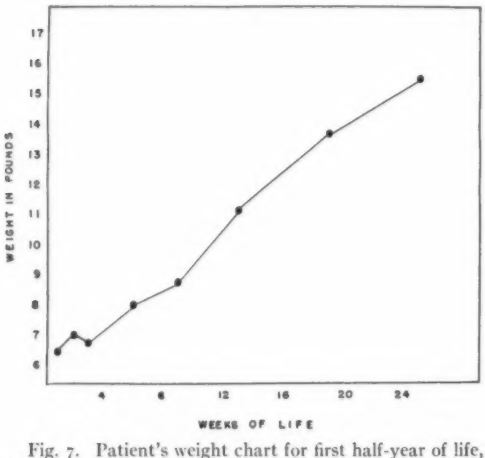

Fig. 7. Patient's weight chart for first half-year of life, indicating satisfactory gain.

DISCUSSION

At least five methods of primary anastomosis have been successfully employed for repair of esophageal atresia. Each of these procedures has certain factors which recommend it as a valuable approach to the establishment of esophageal continuity in infants. Final evaluation of each method is not possible until larger series are available for study, but it is fitting at this time to point out some of the apparent merits or drawbacks of the different forms of anastomosis.

Haight (2,3) has recommended a primary repair whereby the tiny and thin distal segment is telescoped for a short distance into the upper segment in such a way that the entire thickness of the wall of the lower segment is joined by interrupted sutures to the mucosa and the submucosal layers of the upper segment (Fig. 8a). The muscularis of the upper segment is then lapped over and attached by sutures to the muscularis and adventitial structures of the lower segment.

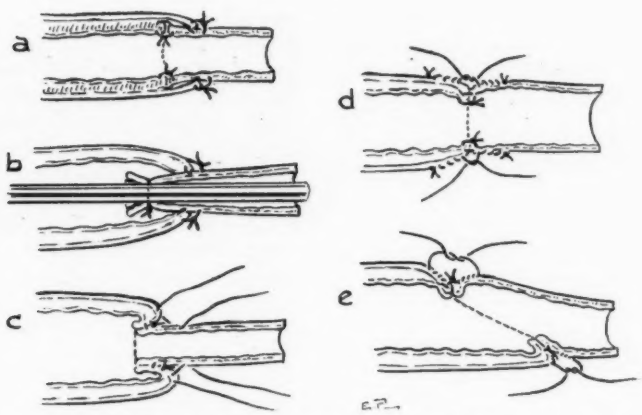

Fig. 8. Schematic drawings of types of esophageal anastomoses. a, Method of Haight. b, Daniel's procedure. c, Humphrey's technique. d, Ladd's method, employing tension sutures to relieve strain on line of union. e, Operation here reported. Ends of multiple bite sutures are tied; opposite ends of these sutures are then being tied to roll in ends of esophagus. Oblique anastomosis.

The outstanding advantage of this method would appear to be in the sleeve-like overlapping of the muscular layers, which obviously should give a great deal of strength to the anastomotic repair. The greatest drawback with this method would probably be the difficulty of placing the first row of interrupted sutures, since the distal segment is usually small, quite friable, and easily torn. Hence, there is considerable chance for the sutures to cut through or pull out, particularly if the segments have to be drawn together under any great tension. Aside from any theoretical disadvantages of the method, Haight's experience to date shows that in 3 cases a brilliant result has been obtained; the babies have not needed gastrostomies and each has been able to take feedings satisfactorily. In 2 patients a fistula developed through the back, but each has healed spontaneously. In another individual, a tracheo-esophageal fistula reopened. Hence, in each of these latter 3 cases it is obvious that some portion of the union had broken down after operation. Nevertheless, Haight's reports have shown more recoveries from direct anastomoses than has any other publication to date.[1]

[1]Since completion of this manuscript one of us (R.E.G.) has attempted several more operations for esophageal atresia by the Haight technique. One of these has survived and at the moment we feel that this is the best method yet devised for esophogeal anastomosis in babies with esophageal atresia.

Daniel employed an ingenious method for the surgical union of the two segments in esophageal atresia. After freeing and opening the upper and lower ends, a catheter was placed in the nose, led down through the upper segment, and threaded through the lower segment into the stomach. This catheter was used for upward traction, after the esophageal end was tied to it. Thus, the lower part of the esophagus could be pulled inside of the upper segment, to which it was then anchored with a number of interrupted stitches joining the muscle layers (Fig. 8b). The chief disadvantage with this procedure would seem to be that the esophagus is completely obstructed until the encircling ligature breaks or until it cuts through the esophageal substance. During this period of total obstruction, saliva can accumulate and possibly spill over into the larynx and trachea. Some of this difficulty might be obviated by very careful nursing care during the postoperative period, so that any accumulated fluid could be frequently sucked out of the mouth and pharynx. It must be pointed out that Daniel was able to overcome a defect in which there was a very long separation between the two esophageal segments. Whether or not such a method will be productive of a higher percentage of strictures at the anastomosis site is as

yet unknown, but in Daniel's single case repeated dilatations have been necessary.

Humphreys has performed primary anastomosis by opening and adequately freeing the two segments and then joining them with interrupted mattress sutures in such a way that the ends are turned inward. His first suture line is then re-enforced by drawing the outer surface of the upper pouch downward to that of the lower segment (Fig. 8c). Humphreys reported 1 patient who survived for 4 months and who was in good condition at the end of that time. The child developed a posterior fistula, but this healed spontaneously. There was some esophageal stricture which required repeated dilatations. However, at the time of the report, all feedings were being taken by mouth in a satisfactory manner.

Most surgeons who have written upon this subject have described the softness and friability of the esophageal tissues. The ease with which sutures cut through and pull out has been noteworthy. With this in mind, Ladd has recommended the placement of four stay sutures in the quadrants of the upper and lower segments. In each of these sutures, a number of bites are taken in the wall so that considerable pull can be made through the thread without having it tear out of the esophagus. When the ends of these stay sutures are tied together, the tension is distributed back for some distance upon either segment (Fig. 8d). Ladd advocated the approximation of the mucosal layer with a few fine silk stitches, tying of the stay sutures, and then re-enforcing the line of anastomosis with a number of small, interrupted mattress stitches. In the 2 cases which he reported neither baby developed a posterior fistula. However, both required repeated dilatations before satisfactory deglutition was obtained.

In the case here reported, several features of the method of anastomosis might be emphasized. First of all, it was believed that a great laxity of structures was essential to the establishment of an anastomosis without undue tension. The upper segment was mobilized as far up as the base of the larynx, thus it could be drawn down with extraordinary facility. The lower segment was freed down to the diaphragm. After this dissection, the entire lower segment became somewhat dark in color and its blood supply was obviously reduced. This development was in direct contrast to the upper segment, which remained pink and apparently of normal viability. The second principle was the establishment of the anastomosis in an *oblique* fashion, in the hope of diminishing the possibility of a postoperative stricture at this site. Third, the tension sutures such as originally described by Ladd were employed in order to obtain a better grasp on the tissues of the two segments. When these were tied, there was an approximation of the abutting ends of the two segments in the region of these sutures, but between these areas the esophageal ends were tented and were separated from each other. Hence, it was decided to tie together the opposite ends of the tension sutures so that the muscular surfaces of the two segments would be rolled inward toward the esophageal lumen. Fourth, the use of mucosal sutures was assiduously avoided because it was thought that the ends of the membranes would be fairly close together and would heal over spontaneously. Fifth, the muscular layers were finally re-enforced with a number of interrupted silk sutures, all of which were placed in a linear direction. While obviously such stitches would not have the holding power of mattress sutures, this latter type of stitch was not used because of the detrimental effect it might have on the local blood supply. In this baby, the mediastinal wound healed without delay and without infection. There was no leakage from the esophagus through the back wound. A gastrostomy was established on the 8th day, but because of the satisfactory function of the esophagus, the gastrostomy was allowed to close on the 17th day. The exceedingly gratifying course of this patient is indicated by the short postoperative hospitalization of only 19 days and also by the satisfactory deglutition during the first year of life. Esophageal dilatations were not necessary in the first year, but were performed after that when more solid food became part of the diet.[1]

[1]Since completion of this report, another baby with esophageal atresia has been operated upon by this technique. This anastomosis was completed in a very satisfying manner, but the child died 48 hours later from an overwhelming pneumonia.

It is needless to emphasize that great delicacy must be employed in the performance of esophageal anastomosis in babies. The tissues, particularly of the lower segment, are extremely fragile and are easily injured. Every effort should be made to handle them with utmost gentleness and to avoid squeezing them with hemostats, forceps, or other instruments. The stay type of suture advised by Ladd provides an admirable handle for traction and for manipulating the esophagus. When one of these stitches has been placed, all subsequent sewing can be accomplished without grasping the esophagus with a metallic instrument. In the case here reported, it seemed to us of considerable importance that the esophagus was not touched with forceps more than three or four times during the entire surgical procedure. To complete such tiny operations successfully, it is necessary to have a few instruments of diminutive size. A small, blunt periosteal elevator or a septum elevator-dissector is essential for stripping the parietal pleura from the thoracic cage and the mediastinal structures. Tissue forceps should be no more than 3 or 4 inches in length and should have delicate, toothless points. Scissors may be curved or straight, but should be no more than 3 or 4 inches in length. Of prime consideration is the type of suture material and the needle upon which it is threaded. We believe that fine braided silk is superior to any other type of suture material. Size No. ooooo has adequate strength and a very small caliber. When attached to a No. 9 Deknatel atraumatic needle, it makes a superb material for use in babies.

The choice of anesthetic agent must, of course, depend upon the circumstances in a given clinic. Local novocain infiltration has been frequently employed; avertin plus novocain has been favorably commented upon; in some instances ether has been preferred. Various authors have condemned general anesthesia, but we are convinced that it greatly facilitates the performance of the operation and need not be productive of shock or untoward reaction. In the case here reported, and in other instances in this hospital, cyclopropane has been the anesthetic of choice. It gives sufficient relaxation, and carries a high concentration of oxygen. When supplied through a tightly fitting face mask, it can be given under positive pressure; if by accident the parietal pleura should be pierced at any time, the lung can be easily expanded. Our selection of cyclopropane has been dependent upon the availability of an expert anesthetist who has had wide experience with its use in babies. Where such conditions do not prevail, local anesthesia would probably be safer.

Discussion has arisen concerning the advantages of leaving a small rubber tube in the reconstructed esophagus. In our case, a No. 8 French catheter was led through the nose, down through the esophagus and into the stomach—and kept there for 8 days. We considered it to have value as a semi-rigid structure for keeping the segments of the esophagus in line. Furthermore, it was enormously useful for feeding purposes during the immediate postoperative period. Conceivably, an inlying catheter can produce pressure necrosis in the anastomotic area, but we are inclined to minimize this danger. Previous experience indicates that some infants will tolerate a tiny rubber tube in the nose for protracted periods of time, while others develop such a violent reaction to it that nasal stuffiness and accumulation of secretions greatly embarrass the baby's breathing. In short, if a catheter is tolerated well, it is probably a valuable therapeutic agent. If, however, too much reaction is set up in the nose or throat, it is folly to keep a tube in place.

The use of a gastrostomy is likewise a moot point. In the present case, gastrostomy was performed 8 days after the esophageal repair, but it was kept open for only a week. This patient fared so well that possibly he could have survived without the gastric opening. In 3 of Haight's patients no gastrostomy was employed. In general, it would seem to us that the establishment of a Stamm gastrostomy under local anesthesia can be such an innocuous procedure that it should be almost universally done a day or two after the esophageal repair; the inlying esophageal catheter could be omitted and all oral feedings could be withheld for several weeks in order

to allow the best possible esophageal healing. While this routine would obviously impose a gastrostomy on some patients who might have survived without it, there would doubtless be improvement in overall results when employed in a series of cases.

The necessity for esophageal dilatations and the frequency with which they must be repeated will depend upon the tightness of any existing stricture and the severity of the dysphagia. The size and the function of the esophageal canal can be observed by a swallow of barium (or lipiodol) and fluoroscopic examination. However, we are convinced that esophageal dilatations should not be performed solely on the basis of any roentgenologic findings which suggest a constriction at the site of anastomosis. Indeed, the indications for dilatation should depend almost entirely upon the subjective symptoms which occur during the ingestion of feedings. One gains the impression that scar tissue (if not too great) at the site of an anastomosis may give trouble for a temporary period, but that the symptoms can become much less as the child grows older and the esophageal lumen becomes greater. In short, the lesser degrees of stricture may be troublesome at first, but they do not necessarily imply that dilatations will be required indefinitely.

SUMMARY

Observations are reported upon a baby with congenital atresia of the esophagus and associated tracheo-esophageal fistula. Surgical correction was undertaken through a right, extrapleural mediastinotomy. The tracheo-esophageal fistula was closed and the two esophageal segments then joined by a long, oblique anastomosis.

The baby was discharged from the hospital 19 days after operation. Esophageal dilatations were not required during the ensuing year, but were performed thereafter. The child is in excellent health at 20 months of age. The surgical method is one which can be employed only when the esophageal segments lie close to one another or when they can be adequately mobilized to allow satisfactory approximation. Under such circumstances, the technique merits further trial in future cases.

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PANCREATIC HETEROTOPIA

Review of the Literature and Report of 41 Authenticated Surgical Cases, of Which 25 Were Clinically Significant

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THE presence of pancreatic tissue in an aberrant location, without connection with the main pancreas, can at the present time no longer be considered merely as a rare and casual postmortem discovery or as an unusual and interesting but incidental finding at operation. In view of the multiple surgical cases of clinical significance reported in the medical literature, it is a condition that should be kept in mind, recognized, and taken into due consideration by the surgeon who operates on the gastrointestinal tract.

In the past 5 years there has been an increased interest, both of the clinician and of the surgeon, in conditions referable to the pancreas. Much study has been done in various sectors in this field. Much of this work has been dedicated to the clinical study and surgical treatment of hypoglycemia and hyperinsulinism. There have been examples reported in which aberrant pancreatic tissue was the site of hyperfunctioning, insulin-producing, benign or malignant neoplastic tissue. The presence of a functioning aberrant islet cell adenoma or adenocarcinoma can possibly explain the enigma of some cases of idiopathic or so-called spontaneous hypoglycemia, in which an exploration does not reveal the presence of any tumor in the main pancreas.

Aberrant pancreatic nodules have at certain times caused embarrassment to the surgeon. At other times, far from being merely an incidental finding, heterotopic pancreatic tissue has been known to be the source of considerable trouble and to be the cause of serious conditions for which a major surgical procedure had to be instituted to obtain relief.

The collection of cases in the literature, especially in the more recent years, has been illustrative and revealing. The reports, however, have all been accounts of isolated instances and no large group of cases has yet been presented from one single source, the largest series being that of Branch and Gross, who presented 24 cases; in only 5 cases, however, was heterotopic pancreatic tissue encountered at operation and in only 4 was it causative of symptoms.

In an endeavor to make a substantial contribution to the casuistics of this subject, we have attempted to make a detailed clinical and pathologic study of all the surgical cases of pancreatic heterotopia found in the records of the Mayo Clinic. There is a relatively large group of cases with clinical significance, especially in the more recent years.

MATERIAL AND METHODS

We reviewed a series of 82 surgical cases. Twenty-five of these were authentic cases (confirmed by microscopic examination) of pancreatic heterotopia in which the heterotopic pancreatic tissue was clinically significant, in that either it was found to be the only or main lesion for which the patient was taken to the operating room or it was one of the lesions contributing to the production of symptoms. These cases are summarized in Table I.

Sixteen cases of the series were authentic cases of pancreatic heterotopia in which the heterotopic pancreatic tissue was merely found incidentally at operation, during the course of a surgical procedure performed for some other lesion.

Abridgment of thesis submitted by Dr. Barbosa to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Surgery.

From the Division of Surgery, Mayo Foundation, and the Section on Surgical Pathology and the Division of Surgery, Mayo Clinic.

TABLE I.—SUMMARY OF AUTHORS' 25 SURGICAL AUTHENTIC CASES OF PANCREATIC HETEROTOPIA WITH CLINICAL SIGNIFICANCE

Case Year Sex Age	Macroscopic and microscopic location of pancreatic heterotopia Histologic evidence of acinar function	Size of mass Pathologic change	Symptoms	Roentgenologic examination	Operation Results
1 1944 F 42	Lesser curvature and posterior wall of stomach. Submucosal and infiltrating muscle layers. No	3.5x3x1.5 cm. (walnut). None	Ulcer history. Pain 1½ hrs. p.c. Loss 15 lbs. weight in 1 yr.	Ovoid tumor mass midportion of stomach. Malignant	Partial gastrectomy; posterior Polya. Good immediate results since operation in June, 1944
2 1944 M 55	Greater curvature prepyloric region of stomach. Submucosa and between muscle bundles. No	1.5 cm. in diameter None	Past history of ulcer symptoms	Filling defect 1.5 cm. in diameter near greater curvature just proximal to pylorus	Excision. Good immediate results since operation in May, 1944. Well 7 mos. p.o.
3 1941 M 44	Stomach; posterior wall greater curvature 1 cm. above pylorus. ? ?	5 mm. in diameter. Shallow recess of mucosa 1.5 cm. in diameter resembling diverticulum, superficial erosion	Recurrent epigastric pain periodically for 12 yrs. At present no relief with diet	Duodenal ulcer	Partial gastrectomy; posterior Polya (grade 3 gastritis with multiple superficial erosions).
4 1937 M 43	Greater curvature of stomach 2 cm. proximal to pylorus. ? ?	1 cm. in diameter None	R.U.Q. pain worse immediately p.c. for 2 yrs. No relief with diet	Polyp 1 cm. in diameter near greater curvature in antrum	Partial gastrectomy; posterior Polya. Well 7 yrs. p.o.
5 1943 M 34	Pyloric end of stomach. Submucosa and infiltrating muscle fibers. No	2x2x1 cm. None	Epigastric distress—2 mos.	Polypoid lesion 2.5 cm. in diameter in pyloric segment of stomach	Partial gastrectomy; posterior Polya. Well 1 mo. p.o. Well 1 yr. 10 mos. p.o.
6 1940 M 38	Posterior wall of stomach just above angle. Submucosa and infiltrating muscular fibers. Yes	3x2 cm. Multiple large cysts seen grossly in mass, dilated ducts	Upper abdominal distress 3-5 hrs. p.c. With food, soda and alkali immediate relief, but diet without result-15 yrs. Loss 20 lbs. Past yr. 1 episode of hemorrhage	Benign tumor in stomach 3 cm. in diameter. Just off lesser curvature above angle. Leiomyoma?	Cautery excision of gastric wall containing tumor. General condition fair. Some epigastric distress weight normal 4 yrs. 8 mos. p.o.
7 1941 F 28	Posterior wall of stomach proximal to pylorus. Submucosa Yes	8 mm. in diameter None	Epigastric distress with nausea 2 hrs. p.c. for 3-5 yrs.	Polyp 1 cm. in diameter on posterior wall of prepyloric region of stomach	Partial gastrectomy; posterior Polya. Well 9 mo. p.o. Well 3 yrs. p.o.
8 1940 M 35	Serosal surface pyloric ring. Subserosa. Yes	3 cm. in diameter None	Periodic epigastric distress with burning and soda relief 4 yrs. Loss 35 lbs., 18 lbs. in 4 mos.	Annular lesion involving pylorus in prepyloric area with duodenum. Malignancy?	Partial gastrectomy; posterior Polya
9 1930 M 49	Stomach, lesser curvature. Submucosa ?	4 cm. in diameter. Aberrant pancreas directly below carcinomatous ulcer (?). Malignant change	Ulcer history 5-6 yrs., hematemesis, tarry stools.	Perforating ulcer lesser curvature of stomach	Partial gastrectomy; posterior Polya. Died 1 yr. 7 mo. p.o.
10 1943 M 43	Stomach, lesser curvature. Submucosa. Yes	1 cm. in diameter. Hemorrhage	Daily ulcer symptoms past 6 mos.	Duodenal ulcer. Ulcer lesser curvature of stomach	Partial gastrectomy; posterior Polya, partial duodenectomy. Satisfactory 6 mos. p.o.
11 M 29	Duodenum. Infiltrating longitudinal muscular fibers. Yes	3x1.5 cm. None (overlying duodenal ulcer).	Epigastric pain, no relief with diet, 2 yrs. 1 hemorrhage. Loss 25 lbs. 1 yr.	Duodenal ulcer, large crater	Partial gastrectomy; posterior Polya
12 1942 M 52	First portion duodenum. Subserosal, submucosal, infiltrating circular muscular fibers Yes	? None (duodenal diverticulum).	Symptoms of bleeding duodenal ulcer 2 yrs. Secondary anemia	Duodenal ulcer	Partial gastrectomy; posterior Polya. Well 6 mos. p.o. Very well 2 yrs. 3 mos. p.o.
13 1939 F 51	Inferior border duodenum, 5 cm. from pylorus. Submucosa Yes	1.5 cm. in diameter None	Epigastric distress 2½ yrs. Temporary relief with nonroughage diet.	Negative stomach and duodenum. Gallbladder normally functioning with stones	Stomach, gallbladder, bile ducts and pancreas normal. Excision of duodenal nodule. Well 2 yrs. 4 mos. p.o. Well 5½ yrs. p.o.
14 1931 M 36	Duodenum 3 cm. below pylorus. Submucosa and infiltrating longitudinal and circular muscular fibers. Yes	5 mm. in diameter. None	Ulcer type of distress 5 yrs. Loss 12 lbs. No relief with diet.	Duodenal ulcer	No evidence of ulcer. Excision of tumor with portion of pyloric muscle. Reconstruction of pyloric outlet. Gained 18 lbs. 2 mos. p.o. Well 8 and 13 yrs. p.o. Working hard.

TABLE I.—SUMMARY OF AUTHORS' 25 SURGICAL AUTHENTIC CASES OF PANCREATIC HETEROTOPIA WITH CLINICAL SIGNIFICANCE—Continued

Case Year Sex Age	Macroscopic and microscopic location of pancreatic heterotopia Histologic evidence of acinar function	Size of mass Pathologic change	Symptoms	Roentgenologic examination	Operation Results
15 1932 F 62	Anterior wall duodenum just below pylorus. Submucosa No	1.5x1x0.8 cm. Necrosis.	Epigastric distress with food relief 15-18 yrs.	Pedunculated polyp approximately 1.5 cm. first part duodenum greater curvature side	Excision of tumor with reconstruction of pyloric outlet. Well 3½ yrs. p.o.
16 1914 F 30	Duodenum 1.3 cm. below pylorus anteriorly ? ?	1.3x1.9 cm. Duodenal ulcer immediately above pancreatic heterotopia.	R.L.Q. pain 1 yr.		Excision of duodenal ulcer with nodule of pancreatic heterotopia and Hincke-Mikulicz pyloroplasty. Well 8 and 18 yrs. p.o.
17 1913 M 50	Anterior lower side of duodenum 2.5 cm. from pylorus ? ?	Small walnut. Inflammatory changes	L.U.Q. pain 2 yrs.	Possible duodenal ulcer	Biopsy of nodule. Severe recurrence of symptoms 1 yr. p.o.
18 1931 F 61	Common duct Yes	Nodule (size?). Marked inflammatory change with lymphocytic infiltration and necrosis	Gas and indigestion 10-15 yrs.	Nonfunctioning gallbladder with stones	Cholecystectomy; drainage of common duct (common duct increased to twice normal size). Well 10 yrs. p.o.
19 1920 M 55	Outlet of common duct. Submucosa ?	2 mm. in diameter. Carcinomatous duodenal ulcer overlying nodule. Malignant change of accessory pancreas (?)	R.U.Q. pain 4 mos. Marked jaundice 3 mos. Loss 27 lbs.	Stomach negative	Gallbladder enlarged 5-6 times normal size. Common duct dilated. Transduodenal excision of nodule and duodenal adenocarcinomatous ulcer. Drainage of gallbladder. Died third day p.o. Pulmonary edema, bronchopneumonia
20 1921 M 34	Gallbladder 2 cm. from cystic duct. Subserosal ?	1x0.6 cm. None	Nausea and regurgitation; intermittent jaundice 2 yrs.	Stomach negative	Cholecystectomy. Still distressed 5 yrs. p.o.
21 1931 F 59	Between posterior wall of stomach and gastrocolic omentum ?	8x5x5 cm. Cystic change.	In 1¾ yrs.: 3 severe spells of upper abdominal pain with nausea and vomiting. Palpable epigastric mass. Loss 42 lbs. in 6 mos.	Stomach negative. Gallbladder nonfunctioning with stones	Accessory pancreatic mass removed. Marsupialization of pancreatic cyst. Gallbladder drained. Well until 2 yrs. p.o. Died from "heart attack"
22 1925 F 20	Transverse mesocolon No	Length—10 cm. Width—4.5 cm., 1.5 cm. Thickness—1.5 cm. Heterotopic pancreatic cyst containing stones, largest 4 mm. in diameter.	Recent epigastric pain with vomiting	Stomach negative	Removal of tumor. Satisfactory 8 yrs. p.o. After trouble with pancreatic lithiasis
23 1942 M 22	Abdominal wall (in omphalomesenteric cyst, 2 cm. in diameter). Submucosa of small bowel epithelium Yes	Cyst 2 cm. in diameter. Fat necrosis with scattered foreign body giant cells in surrounding tissue	Intermittent soreness, tumor and drainage in umbilical region since childhood		Removal of cyst intact. Excellent health. No recurrence of symptoms 2 yrs. 4 mos. p.o.
24 1939 M 27	Tip of Meckel's diverticulum. Submucosa Yes	1 cm. in diameter. None	Periodic attack of "biliousness" 2 yrs.	Gallbladder normally functioning	Removal of diverticulum. Appendectomy. Well 4 yrs. p.o.
25 M 4 mos.	Tip of ileal diverticulum. Submucosa No	1.5x0.6x0.5 cm. Necrosis and hemorrhage	Crying and vomiting 7½ hrs. Enterorrhagia. "Sausage-like" mass palpated over right flank		Resection 25 cm. gangrenous bowel. Witzel enterostomy. Died 5 hrs. p.o. Shock

Fourteen cases were unconfirmed cases of pancreatic heterotopia which we interpreted as clinically significant. The heterotopic pancreatic tissue, diagnosed grossly as such by the surgeon in these cases, seemed to be the cause of persistence or recurrence of symptoms after an operation performed on an organ bearing lesions which could not explain the symptoms present.

Twenty-seven cases were unconfirmed cases

TABLE II.—CASES OF PANCREATIC HETEROTOPIA RECORDED IN THE LITERATURE SINCE FAUST AND MUDGETT'S REVIEW IN 1939

Year	Author	Organ	Cases
	Meyer May*	Stomach (Ca., Ins.)†	1
1937	White and Gildea*	Near pancreas (Ins.)†	1
	Lapidari*	Stomach	1
	Picco*(47)	Stomach (P.O.)†	1
1938	Black and Packard*	Meckel's diverticulum	1
	Canger*	Stomach	1
	Guidotti	Duodenum	1
	Gottlieb	Umbilical region	1
	Cruickshank	Miscellaneous	1
	Saupe	Stomach	1
1939	Picco(48)	Stomach	1
	Hintzsche	Duodenum	1
	Natale and Caccia	Duodenum	1
	Martin and Guichard	Miscellaneous	2
	Picchio	Stomach	1
	Marinucci	Mesenteric root (cyst)	1
	Granet	Stomach (P.O.)†	1
	Cazzola	Duodenum	1
		Jejunum	3
1940	Thorsness	Gallbladder	1
	Derbyshire	Stomach	3
		Duodenum	2
		Meckel's diverticulum	1
		Miscellaneous	6
	Hoelzer	Duodenum (P.V.)†	1
	Jacobson	Gallbladder	1
	Coppola	Miscellaneous	1
	Roton, Mieng and Auburtin	Spleen (cyst)	1
	Krieg	Stomach (P.O.)†	1
	Cabot(6)	Stomach	1
1941	Masciottra and Vinas Urquiza(40)	Duodenum	1
	Ballinger	Liver (Ca., Ins.)†	1
	Rudd and Walton	Gastrosplenic omentum (Ins.)†	1
	Morison	Duodenum (Div.)†	3
		Meckel's diverticulum	1
	Masciottra and Vinas Urquiza(41)	Duodenum	1
	Smith	Duodenum (Ins.)†	1
1942	Jorge and Latienda	Jejunum	1
	Vinas Urquiza	Duodenum	1
	Duff, Foster and Bryan	Duodenum (Ca., P.O.)†	1
1943	Chapman and Mossman	Duodenum	1
	Holman, Wood and Stockton	Near pancreas (Ins.)†	2
	Warren and Emery	Duodenum (Div.)†	4
	Castro Barbosa, Dockerty and Waugh	Stomach	14
		Duodenum	11
		Jejunum	5
1945		Ileum	1
		Meckel's diverticulum	2
		Umbilical region	1
		Gallbladder	1
		Miscellaneous	6
Total cases			101

*Cases not mentioned in Faust and Mudgett's review but recorded in the literature prior to 1939.
†Ca. = malignant lesion in heterotopic pancreatic tissue.
Ins. = producing insulin and causing hypoglycemia.
Div. = diverticulum of the duodenum.
P.V. = papilla of Vater obstructed by accessory pancreatic gland.
P.O. = pyloric obstruction.

of pancreatic heterotopia in which the heterotopic pancreatic tissue, diagnosed grossly by the surgeon as such, was found incidentally during the course of an operation performed for some other surgical condition and was thought not to be of clinical significance.

GENERAL CONSIDERATIONS

Definition. Pancreatic heterotopia is defined as being the presence of pancreatic tissue outside its usual or habitual location and without anatomic relation either of continuity or of vascularization with the pancreas proper.

Literature. A complete review was made first of the early literature and second of the recent literature (Tables II and III). As precisely as we can determine, from 1727 to March, 1944, approximately 430 cases have been recorded in the literature, to which we add the cases of our series (Table III), which includes 41 authentic cases and 41 unconfirmed cases.

Embryology and hypotheses of origin. Arey gave a very clear description of the organogenesis of the pancreas. The classical descriptions are generally in agreement as far as the number and general topography of the pancreatic anlagen are concerned. They differ, however, when it comes to describing the phases through which the anlagen go in order to form the definitive pancreas. In 1939 Delmas presented his findings after following the evolution of the pancreas on reconstructions made by Born's method on human embryos from 5 to 27 millimeters in length. Delmas concluded that the total pancreas is completed at the 27 millimeter stage. According to his research, which was the most recent and thorough work that we found on this subject, the dorsal pancreas forms the head of the pancreas (primitive dorsal anlage) and the body and tail of the pancreas (bud from the dorsal anlage). The ventral pancreas forms the preduodenal process, the pancreas minor of Winslow, and reinforces the dorsal part of the head of the pancreas. The ventral pancreas is the only anlage that tends to encircle the duodenum.

Practically all the concepts of the etiology of heterotopic pancreatic tissue maintain that

TABLE III.—SUMMARY OF ALL RECORDED CASES*

Location	Warthin 1904	Horgan 1921	Simpson 1927	Hunt and Bonesteel 1934	Poppi 1935	Faust and Mudgett 1940	Present study from table 2†		Total	Per cent
							From literature, March, 1944	Authors' cases		
Wall of stomach	14	8	25	12	21	15	12	13	120	25.5
Wall of duodenum	10	4	14	12	44	21	15	10	130	27.7
Wall of jejunum	13	13	10	3	20	8	4	4	75	15.9
Wall of ileum	1	1	2	0	6	3	0	0	13	2.8
Diverticulum of stomach	1	0	2	0	0	0	1	1	5	1.1
Diverticulum of duodenum	0	2	0	1	2	2	5	1	13	2.8
Diverticulum of jejunum	0	0	0	0	1	0	0	1	2	0.4
Diverticulum of ileum	2	3	4	4	0	0	0	1	14	3.0
Meckel's diverticulum	3	1	6	3	0	7	3	2	25	5.3
Umbilical fistula	1	0	0	0	0	0	1	1	3	0.6
Mesentery	1	0	0	0	2	0	1	0	4	0.8
Omentum (gastrohepatic, gastrocolic, gastrosplenic)	1	0	0	0	4	0	1	2	8	1.7
Spleen	0	0	0	0	1	0	1	0	2	0.4
Splenic capsule	0	1	2	0	0	0	0	0	3	0.6
Gallbladder	0	0	1	1	1	0	2	1	6	1.3
Cystic duct	0	0	0	0	1	0	0	0	1	0.2
Common duct	0	0	0	0	0	0	0	2	2	0.4
Liver	0	0	0	0	0	0	1	0	1	0.2
Transverse mesocolon	0	0	0	0	1	0	0	1	2	0.4
Near pancreas	0	0	0	0	0	0	3	0	3	0.6
Mediastinal teratomatous cyst	0	0	0	0	1	0	0	1	2	0.4
Miscellaneous	2	1	1	0	21	2	10	0	37	7.9
Total cases	49	34	67	36	126	58	60	41	471	100
							101			
Individual contribution	2	2	1	1	3	1	41			

*Branch and Gross in 1935 reported 24 cases of their own, besides an additional 10 from the literature.
†We did not include 41 surgical cases of pancreatic heterotopia without microscopic confirmation.

this anomaly is antenatal in origin. It is evident that one single concept does not explain all cases, however much basis of truth it possesses. Our attitude in regard to these hypotheses is eclectic. Of those concepts presented, three deserve mention for being the ones that seem most logical to us and that are based on embryologic knowledge; namely, Horgan's, Lordy's, and Warthin's concepts. Horgan expressed the belief that before the coalescence between the two anlagen takes place during the partial circumrotation of the posterior and anterior pancreatic anlagen, when there is a migration of the body upward, the branching ducts, as a result of the organs being packed together, come into contact with the walls of the mesentery, stomach, or intestine growing in the opposite direction. On these they become engrafted, because of noninflammatory adhesions of fetal life. Later during the growth and movements of the gland the attached part is pulled off and may continue to live incorporated as a graft in the gastric, duodenal, or intestinal wall or mesentery. The germinative cells, from which all the histologic units of the pancreas can develop, are present in these buds or attached portions derived from the primitive anlage.

TABLE IV.—INCIDENCE OF HETEROTOPIC PANCREATIC TISSUE IN CONSECUTIVE NECROPSIES

Author	Necropsies performed	Heterotopic pancreatic tissue, cases	Per cent
Opie	1,800	10	0.6
Horgan	321*	2	0.6
McGill	1,970	21	1.1
Derbyshire	8,913	104	1.2
Kremer	467	6	1.3
Katsurada	329	6	1.8
Feyrter(17,18)	1,100	25	2.3
Mouchet	200	5	2.5
Letuelle	180	10	5.6
Clinic series			
1939	585	6	1.0
1940	576	10	1.7
1941	464	11	2.4
1942	528	11	2.1
1943	632	10	1.6
Total†	2,785	48	1.7

*Entire gastrointestinal tract opened in 314 cases.
†Of clinic series.

TABLE V.—PRECISE HISTOLOGIC LOCATION OF THE HETEROTOPIC PANCREATIC TISSUE IN 26 CASES

Location	Symptoms	No symptoms	Total cases	Per cent
In submucosa only	9	5	14	54
In submucosa and infiltrating muscular fibers	5	1	6	23
Between muscle fibers only	1	1	2	8
On the subserosa or serosal surface only	2	1	3	11
In the submucosa between the muscle fibers and in the subserosal tissue	1	0	1	4
Total	18	8	26	100

This "graft" may find suitable environment and continue to live and develop into a small separate piece of pancreatic tissue constituting a pancreatic heterotopia with all the functions of the normal pancreas.

Lordy explained the presence of an accessory pancreas by stating that it is due to persistence or incomplete regression of the left ventral anlage, which is normally destined to atrophy. Warthin described his concept of the origin of pancreatic heterotopia as follows: "It is probable that accessory pancreatic tissue is formed from lateral budding of the rudimentary pancreatic ducts as they penetrate the intestinal wall, the mass of pancreatic tissue thus formed being snared off and carried by the longitudinal growth of the intestine either upward or downward."

Incidence. The incidence of heterotopic pancreatic tissue not only at necropsy but at operation was studied from reports in the literature and from our own findings in the surgical records and those of the Section on Pathologic Anatomy of the Mayo Clinic. It is seen that the incidence at necropsy varies from 0.6 per cent to 5.6 per cent of routine necropsies (Table IV). At operation heterotopic pancreatic tissue is found once in approximately every 500 operations in the upper abdominal region.

There is a higher incidence of surgical cases in the fourth, fifth, and sixth decades of life than in other decades but the anomaly has been found in patients of all ages both young and old, including infants and newly born. In our series the youngest patient was 4 months and the oldest patient was 64 years of age.

Location. We particularly endeavored to determine the usual and unusual locations of pancreatic heterotopias. The duodenum, stomach, and jejunum are the most common sites, with an incidence for the three sites of almost 70 per cent: 27.7 per cent for the duodenum, 25.5 per cent for the stomach, and 15.9 per cent for the jejunum (Table III). All the other unusual locations are mentioned in Table III.

Morphology. Heterotopic pancreatic tissue usually presents itself as a single, firm and, when visible, yellowish (light yellow or cream color) or white, opaque, lobulated, round, or irregular node with granular surface. The maximal diameter of the node is usually 1 to 4 centimeters. Its appearance is like that of the pancreas itself or of a salivary gland. Larger masses may be found (Fig. 1).

The histologic picture of heterotopic pancreatic tissue is frequently the same as that of the pancreas itself, with acini forming lobules with ducts and islands of Langerhans (Fig.

TABLE VI.—SUMMARY OF 6 CASES* OF PANCREATIC HETEROTOPIA ASSOCIATED WITH HYPOGLYCEMIA AND HYPERINSULINISM, COLLECTED BY THE AUTHORS FROM REPORTS IN THE LITERATURE

Case number and author	Patient, sex and age, years	Symptoms	Operative findings	Pathologic findings	Results
1. Vecchi 1914 (one case)		No clinical history. Hyperinsulinism?	Large tumor near tail of pancreas	Large islet cell tumor (malignant adenoma) arising in accessory pancreas	
2. Fanta 1937 (one case)	Male 37	*Hypoglycemia and hyperchlorhydria	Removal of walnut sized nodule of aberrant pancreas in duodenum	Heterotopic pancreatic tissue, not adenomatous	Partial relief from symptoms
3. Meyer May Apr., 1937 (one case)	Female 28	Hyperglycemia. Loss of weight. Abdominal tumor. Roentgenogram suggested tumor between stomach and colon—pancreatic cyst?	Cystic tumor in stomach wall with communication with pylorus with gastric ulcer. No communication with pancreas. Removal of tumor and pylorectomy	Cystadenocarcinoma of aberrant intragastric pancreas (epitheliomatous masses with cells like Langerhans cells). Gastric ulceration	Recovery
4. White and Gildea Aug., 1937 (one case)	Female 32	*Hypoglycemia. Four episodes mental confusion, restlessness, headache, dizziness and trembling. No result with medical treatment	Removal of calcified tumor outside pancreas, in connective tissue surrounding it. No connection with pancreas	Calcified adenoma 1x1.5 cm. with islet cell tissue. No mitotic figures	Complete relief. Gain in weight
5. Ballinger Aug., 1941 (one case)	Male 53	*Very low hypoglycemia (proved specifically not to be hepatogenic). Fasting—mental confusion and faintness, convulsions and coma (worse with metastases)	Tumor 10x6x6 cm. found in retroperitoneal area between upper border head of pancreas and spigelian lobe of liver. Infiltration of liver. Irremovable. Biopsy	Metastasizing insular carcinoma of aberrant pancreatic tissue in liver, containing hypoglycemia-producing substance	Hypoglycemic episodes continued, necessitating large amount of glucose for relief
6. Rudd and Walton Oct., 1941 (one case)	Male 29	*Stupor—unconscious with low blood sugar level. Dramatic recovery with glucose (Parkinson's syndrome). Hypoglycemia	Nodule in gastrosplenic omentum 2.5 cm. from tip of tail of pancreas. Firm, round, 1.3 cm. in diameter. No connection with the main gland	Islet adenoma (pink on cut surface)	Physical and mental improvement. Normal glucose tolerance test
7. Smith Feb., 1942 (one case)	Female 45	*Weakness—faint. Appetite for sweets. Hypoglycemia. Relief of symptoms with food	Excision of nodule from descending duodenum	Nodule 2x1.5x0.5 cm. Weight 1.5 gm. with acini, ducts and diffuse islet cells (not adenomatous)	Weakness better. No hunger. Gained 20 lbs.
8. Holman, Wood, and Stockton Aug., 1943 (2 nodules)		*Dizziness and weakness with inadequate feeding and strain. Intermittent episodes of acute mental upset, irresponsiveness and coma. Hypoglycemia	*1st operation:* Excision of bluish nodule near end of tail of pancreas, together with a portion of pancreas. *2nd operation:* Excision of round bluish node between pancreas and spleen	*1st nodule:* Islet cell adenoma, 0.7 cm. in diameter. *2nd nodule:* Islet cells; nodule 2 cm. in diameter	No relief from first operation. Patient well 1 yr. after second operation
9. Holman, Wood, and Stockton Aug., 1943 (one case)	Female 61	Node found incidentally	Node in proximal duodenum found *incidentally* during necropsy, following death from peritonitis	Submucous islet cell adenoma	Died

*This table also includes Vecchi's case, as well as one case of islet cell adenoma without hypoglycemia and one case of islet cell cystadenocarcinoma with hyperglycemia, from the literature.

2). There may, however, be a lack of one or another histologic element of the normal pancreas.

In the majority of the cases reported as well as in our own cases the type of mucosa directly overlying the heterotopic tissue is the same as the type of mucosa normally corresponding to that particular portion of the gastrointestinal tract where the heterotopic pancreatic tissue is situated. We were not convinced of any direct relation, continuity, or transition between the glands and ducts of the mucosal epithelium and the acini and ducts of the heterotopic pancreatic tissue. The only possibility of indirect connection would be by means of the excretory ducts of the heterotopic pancreatic tissue emptying into the lumen of the gastrointestinal tract through the ducts of the mucosal epithelium. The commonest histologic location of heterotopic pancreatic tissue was found to be the submucosa alone, with an incidence of 53.8 per cent. The second most common type of involvement was infiltration between the longitudinal or circular muscular fibers or both, with an incidence of 23 per cent. The least common location was the serosal surface (Table V).

TABLE VII.—PRODUCTION OF SYMPTOMS, BY THE HETEROTOPIC PANCREATIC TISSUE, ACCORDING TO ITS LOCATION IN THE STOMACH, DUODENUM, OR JEJUNUM, IN 27 AUTHENTIC AND 37 UNCONFIRMED CASES FROM AUTHORS' SERIES OF PANCREATIC HETEROTOPIAS, IN WHICH THE FOREGOING LOCATIONS WERE FOUND

Location	With symptoms			Without symptoms			Total
	Authentic cases	Unconfirmed cases	Total	Authentic cases	Unconfirmed cases	Total	
Stomach*	9	2	11	4	0	4	15
Duodenum†	6	12	18	4	17	21	39
Jejunum‡	0	0	0	4	6	10	10
Total	15	14	29	12	23	35	64

*There was also one case of pancreatic tissue in a gastric diverticulum (with symptoms).
†There was also one case of pancreatic tissue in a duodenal diverticulum (with symptoms).
‡There was also one case of pancreatic tissue in a jejunal diverticulum (without symptoms).

Physiology. Special staining methods were utilized to determine whether or not heterotopic pancreatic tissue secretes enzymes. Mallory's (36,37) phosphotungstic acid-hematoxylin stain was most satisfactory. Histologic evidence of acinar function in our cases was present in 76 per cent. In these cases, refractile zymogen granules could be seen in the apex or base of the acinar cells or scattered all over inside these cells (Fig. 3). An investigation was carried out in order to determine what influence this external secretion could have on the gastric acidity. As a result of the analysis of gastric contents in our cases, we cannot conclude that there is any significant deviation to indicate alkalinization of the gastric acidity brought about definitely by functioning heterotopic pancreatic tissue in the stomach wall. We did not carry out a histologic study with any special staining methods for types or functional activity of cells in the islands of Langerhans but we have no reason to disbelieve in the functional activity of the islets of normal appearance in heterotopic pancreatic tissue. We wonder whether heterotopic pancreatic tissue may not, to a certain extent, constitute a somewhat similar circumstance to a graft of a small fragment of pancreatic tissue.

It is of great practical importance, especially to the surgeon, to note that hyperinsulinism and hypoglycemia have been observed associated with extrapancreatic, insulin-producing, islet cell adenomas and adenocarcinomas (Table VI). If, therefore, exploration is being carried out in a case of hypoglycemia with definite "Whipple's essential triad" and, after a thorough search, no tumor is found in the pancreas, the surgeon should look for heterotopic pancreatic

TABLE VIII.—FORTY-THREE CASES OF PANCREATIC HETEROTOPIA COLLECTED FROM THE LITERATURE BY POPPI IN 1935 IN WHICH SYMPTOMS WERE PROVED, AT OPERATION, TO BE PRODUCED BY THE HETEROTOPIC PANCREATIC TISSUE

Clinical diagnosis and percentage	Location of heterotopic pancreatic tissue					Total
	Stomach	Duodenum	Jejunum	Gallbladder	Meckel's diverticulum	
17 cases gastric or duodenal ulcer 39.53%	7	0	1	1	1	10*
10 cases gastropathy 23.25%	9	2	0	0	0	11†
7 cases cholelithiasis, hepatic colic or right upper quadrant syndrome 16.27%	3	3	0	1	0	7
9 cases pyloric neoplasm 20.23%	9	0	0	0	0	9
Total	28	5	1	2	1	37

*Only the 10 cases in which no ulcer was found are included.
†In 1 case the location was both gastric and duodenal. These two notes account for the total number of 37 instead of 43 mentioned in the title of the table.

Fig. 1. Case 22, Table I. Mass of heterotopic pancreatic tissue removed from the mesentery of the transverse colon. Its dimensions were as follows: length, 10 centimeters; width, largest (globular end) 4.5 centimeters, smallest (neck) 1.5 centimeters; thickness, 1.5 centimeters. A cyst was found at the globular end of the elongated mass of heterotopic pancreatic tissue. The cyst contained stones (largest 4 mm.) and sandy material. Grossly at operation the mass gave the impression of a lymphosarcoma or of tuberculosis of lymph nodes.

tissue in its most common locations and also in such of the unusual sites as permit exploration.

Pathology. Pathologic changes have been found in heterotopic pancreatic tissue itself, in the surrounding tissues, or in both. Heterotopic pancreatic tissue presents the same pathologic changes as the pancreas; namely, cysts, pancreatitis, hemorrhage, necrosis, and neoplastic change (benign and malignant). Data on 3 cases of cyst formation in heterotopic pancreatic tissue are presented in Table I (Fig. 4). An investigation was carried out to determine the presence of dilatation of the ducts in pancreatic dystopias. The ducts were

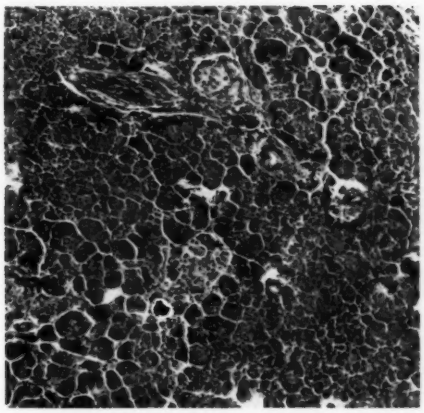

Fig. 2. Case 1, Table I. Portion of a mass of heterotopic pancreatic tissue measuring 3.5 by 3 by 1.5 centimeters on the posterior wall and lesser curvature of the stomach, showing acini and islands of Langerhans. Hematoxylin and eosin. ×88.

found to be dilated in a large number of cases. Both benign and malignant changes in heterotopic pancreatic tissue have been observed. We feel that malignant change is more likely to take place in heterotopic pancreatic tissue than in the normally placed pancreas. The heterotopic pancreatic tissue is not always completely formed and differentiated. Both benign and malignant change would possibly be more likely to take place in an incompletely developed and less differentiated tissue in an aberrant location where it is subject to irritation than in a normal tissue in its usual site. There have been cases in the literature in which the malignant change had its origin traced back to heterotopic pancreatic tissue. It seems that there is little basis to believe in any connection between heterotopic pancreatic tissue and the histogenesis of carcinoids.

Pathologic changes sometimes occur in the tissues adjacent to the heterotopic pancreatic tissue; namely, fat necrosis, inflammation, hemorrhage, ulceration and diverticulum formation. All the foregoing pathologic changes were studied fully, especially ulceration of the mucosa overlying the dystopic pancreatic tissue, which may be the cause of gastroduodenal ulcers in a small number of cases. In such cases conservative surgical treatment

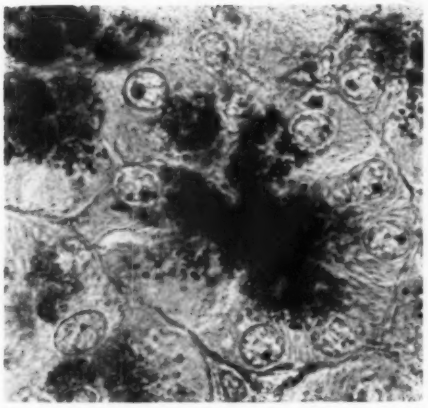

Fig. 3. Case 1, Table I. Portion of a mass of heterotopic pancreatic tissue in the stomach wall. Staining method: Mallory's phosphotungstic acid-hematoxylin stain, with oil immersion lens. ×1053. The individual zymogen granules can be seen agglomerated at the apex of the acinar cells.

is indicated; namely, simple local excision of the ulcer together with the underlying misplaced pancreatic tissue mass. Data on 3 cases are presented in Table I. Formation of a diverticulum brought about by heterotopic pancreatic tissue was studied; data on 3 cases in which symptoms were caused by these lesions will be found in Table I.

Clinical significance. In 25 (61 per cent) of the 41 authentic cases of pancreatic heterotopia the heterotopic pancreatic tissue was proved at operation to have been the only

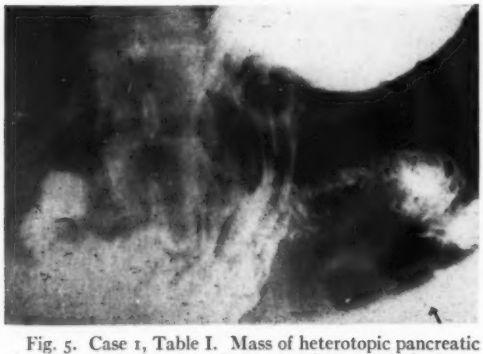

Fig. 5. Case 1, Table I. Mass of heterotopic pancreatic tissue measuring 3.5 by 3 by 1.5 centimeters on the lesser curvature and posterior wall of the stomach giving a roentgenologic image of an ovoid mass, in midportion of stomach; its malignant nature could not be excluded roentgenologically.

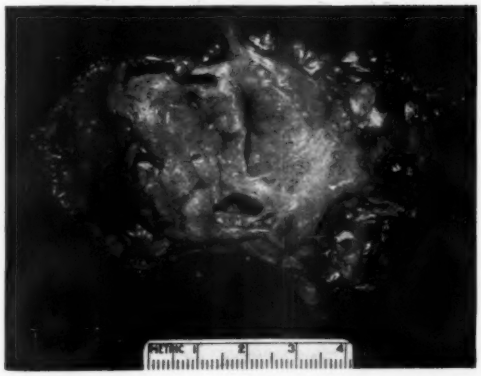

Fig. 4. Case 6, Table I. View from the serosal side of a portion of gastric wall, measuring 7.5 centimeters in diameter (excised with cautery), containing an intramural mass of heterotopic pancreatic tissue, measuring 3 by 2 centimeters. Cysts can be seen grossly in the pancreatic tissue.

lesion, the principal lesion or at least one of the lesions causative of symptoms for which the patient was submitted to surgical intervention. Of the 25 authentic cases in which there were symptoms, it was seen that in 9 (36 per cent) the heterotopic pancreatic tissue was located in the gastric wall. The incidence in this location in all authentic cases, with or without symptoms, was 31.7 per cent. In 6 (24 per cent) of the cases in which there were symptoms the location was in the duodenal wall. The incidence in this location in all authentic cases was 24.4 per cent. There were no cases with jejunal location presenting symptoms but the incidence in this location in the authentic cases without symptoms was approximately 10 per cent. (Tables VII and VIII). For the cases in which heterotopic pancreatic tissue occurred in other locations see Table III. In most of the cases of pancreatic heterotopia in which there were symptoms, the location was either gastric or duodenal. Proportionately, the cases of heterotopia with gastric location contribute more than the ones with duodenal location to the number of cases with symptoms. In 13 cases reviewed there was persistence of symptoms possibly because of failure to remove a supposed pancreatic heterotopia at operation.

Symptomatology. There is no single symptom complex for pancreatic heterotopia. The symptoms, of course, vary according to the

Fig. 6. Case 1, Table I. Mass of heterotopic pancreatic tissue measuring 3.5 by 3 by 1.5 centimeters on the lesser curvature and posterior wall of the stomach. The patient gave a history simulating that of duodenal ulcer and a loss of weight. The tumor was mistaken clinically, roentgenologically, and at operation for an adenocarcinoma of the stomach. The tumor had been sectioned for examination when this picture was taken.

different locations in which heterotopic pancreatic tissue may be found. The symptoms produced, however, are generally similar to those produced by gastroduodenal lesions; namely, symptoms of gastric ulcer, duodenal ulcer, pyloric obstruction, cholecystitis, obstruction of the common duct, chronic or acute appendicitis, or indeterminate digestive symptoms. The group of authentic cases in which there were symptoms was reviewed in subgroups divided according to location and the complication or disturbance that the anomaly caused. There were 10 authentic cases of pancreatic heterotopia with a gastric location and presenting symptoms which were caused by the heterotopic pancreatic tissue, as proved by the relief of the symptoms after its removal. Data on 6 cases are presented in Table I (Figs. 5, 6, 7, 8, and 9). There were 7 authentic cases of pancreatic heterotopia with duodenal location and presenting symptoms

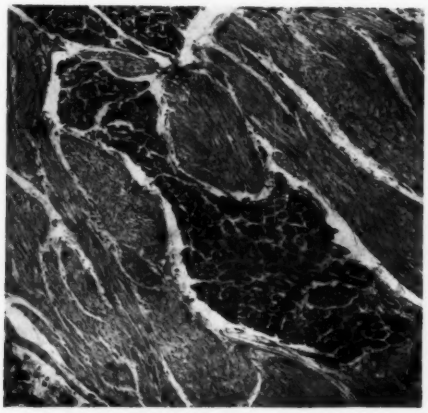

Fig. 7. Case 1, Table I. Heterotopic pancreatic tissue mass, showing pancreatic tissue extending between the muscular bundles. Grossly the tumor seemed to infiltrate the muscular coat of the stomach. Hematoxylin and eosin. ×70.

which were caused by the heterotopic pancreatic tissue, as proved by the relief of symptoms after its removal in practically all the cases. Data on 3 cases are presented in Table I (Fig. 10).

Among our 10 cases of pancreatic heterotopia with a gastric location there was 1 case in which pyloric obstruction was observed.

Fig. 8. Case 2, Table I. Gastric nodule of heterotopic pancreatic tissue 1.5 centimeters in diameter producing a filling defect near the greater curvature just proximal to the pylorus; it appeared like a leiomyoma grossly at operation.

Fig. 9. Case 7, Table I. Nodule of heterotopic pancreatic tissue measuring 8 millimeters in diameter in the submucosa of the posterior wall of the prepyloric region of the stomach. The overlying gastric mucosa is pitted.

Fig. 10. Case 15, Table I. Nodule of heterotopic pancreatic tissue, measuring 1.5 by 1 by 0.8 centimeter in the anterior wall of duodenum immediately below pylorus. The mass looked like a fibroma grossly at operation.

Data on this case are presented in Table I (Figs. 11 and 12). Seventeen cases of pyloric stenosis which were secondary to the presence of heterotopic pancreatic tissue were collected by Krieg from the medical literature in 1939 and published in 1941. We found in the literature 5 additional cases of heterotopic pancreatic tissue causing pyloric obstruction from the time of Krieg's review in 1939 up until March, 1944. Krieg mentioned a group of 23 cases of Poppi's series which he interpreted as having been produced by local spasm of the intestinal wall. In his opinion the difference between the cases of stenosis and those of spasm is that of time and the degree of irritation.

Hypertrophy of the muscular coat was evidenced grossly and microscopically in 11 out of 19 authentic cases of our series of pancreatic heterotopia in the gastrointestinal tract. In our series of authentic cases, there were 2 cases of Meckel's diverticulum containing heterotopic pancreatic tissue. Data on a case of ileal intussusception brought about by an ileal diverticulum containing pancreatic tissue will be found in Table I. Data on a case of pancreatic heterotopia in the wall of the gallbladder are presented. This case is of interest in the light of Colp and Doubilet's studies on the clinical significance of pancreatic reflux. Data on a case of obstruction of the common duct caused by heterotopic pancreatic tissue are presented in Table I. The possibility of duodenal adenocarcinoma arising in dystopic pancreatic tissue in the ampulla of Vater and in the papilla of Santorini is suggested. A study of the pathogenesis of the disturbances and symptoms caused by heterotopic pancreatic tissue was made. The pathologic changes have an influence on the production of symptoms.

Diagnosis. The clinical, the roentgenologic, the operative, and the pathologic diagnosis of pancreatic heterotopia were reviewed. Of the cases in which the heterotopic tissue was in a gastric location the diagnosis of a benign

Fig. 11. Case 8, Table I. Annular mass of heterotopic pancreatic tissue on the serosal surface of the pyloric ring. The roentgenologic report was as follows: "Annular lesion involving pylorus, prepyloric area and base of duodenum; shallow ulceration; impossible to exclude malignancy."

Fig. 12. Case 8, Table I. Specimen: 12 centimeters of stomach and 1.5 centimeters of duodenum. Heterotopic pancreatic tissue forming an annular mass, 3 centimeters in diameter, on the serosal surface of the pyloric ring. The tumor in the picture is included between the points of the two arrows. It was causing pyloric obstruction and loss of weight; clinically, roentgenologically and grossly at operation it was mistaken for an adenocarcinoma of the stomach.

tumor was made in 50 per cent, of ulcer in 20 per cent, and of malignant tumor in 20 per cent. The mass was missed in 10 per cent. In only 1 of the cases in which the location was duodenal was the diagnosis of duodenal tumor made. In all the others the roentgenologic diagnosis of duodenal ulcer was made although in only 1 was an ulcer actually present. The preciseness of the roentgenologist's diagnosis of gastric polyps may be seen from his reports in 6 of our cases in which the masses were of relatively minute proportions. The diagnosis of a gastric or duodenal polyp is the nearest that one can actually get to the precise and final diagnosis made by the pathologist, although in 3 cases of our series the exact nature of the mass was suspected. Apparently, analysis of gastric contents is of no avail in determining possible alkalinity or reduced acidity of gastric contents due to alkalinization of the gastric juice from pancreatic secretion flowing from heterotopic pancreatic tissue, although this possibility should be kept in mind. Gastroscopy might possibly be an aid in the diagnosis by confirming the roentgenologic finding or by revealing the tumor to be intramural, covered by normal mucosa and not ulcerated as in gastric carcinoma. When visible on the serosal surface, a pancreatic heterotopia is grossly recognizable but there should always be a confirmative diagnosis by the pathologist. In 18 surgical cases of pancreatic heterotopia in which a notation was made of the surgeon's impression from gross examination we reviewed the operative diagnosis made prior to the pathologist's report. In approximately 29 per cent the pancreatic heterotopia gave the impression of a malignant lesion. In 50 per cent the diagnosis of a benign lesion was made. In a little more than 22 per cent the nature of the mass was recognized correctly as being

TABLE IX.—SURGICAL PROCEDURES PERFORMED IN 25 CASES OF PANCREATIC HETEROTOPIA

Surgical procedure	Cases
Biopsy	1
Partial gastrectomy	10
Removal of tumor	10*
Resection of gangrenous bowel (intussusception)	1
Cholecystectomy	2†
Diverticulectomy and appendectomy	1
Total	25

*Marsupialization of an associated pancreatic cyst was performed in 1 case, cholecystostomy and exploration of the interior of gallbladder in 1 case and in 1 case transduodenal removal of duodenal adenocarcinoma and cholecystostomy.
†Exploration of the common duct was performed in 1 case.

heterotopic pancreatic tissue. The pathologist's diagnosis based on examination of frozen sections at the time of operation is essential. The correct diagnosis was promptly made in practically all the cases.

Surgical treatment. There are two circumstances in which a pancreatic heterotopia may be found at exploration: it is either causative of symptoms or it is only an incidental finding. In Table IX we listed the operative procedures performed in 25 cases of our series of pancreatic heterotopia that were clinically significant. In no case was persistence or recurrence of symptoms observed following the complete radical or conservative removal of the pancreatic heterotopia when this lesion was the only cause of the complication and referred symptoms. In some of the cases of our series a more conservative operative procedure rather than gastrectomy could have been performed probably with equally good final results, had it been possible for the surgeon to know that he was dealing with a benign lesion. In only 1 case in our series did a patient die from a complication associated with a pancreatic heterotopia; namely, ileal intussusception.

When the pancreatic heterotopia is located in the stomach or duodenum, simple local excision, when feasible, is sufficient to bring about relief of symptoms. At times careful duodenal reconstruction or pyloroplasty may have to be carried out. Since, as is shown by the abstracts of the case records, in most instances a roentgenologic diagnosis of ulcer, tumor, carcinoma, or polyp was made preoperatively, it is understandable why in 10 instances partial gastrectomy was chosen by the surgeon as the procedure to be performed. It would be difficult to tell by palpation the nature of the lesion and biopsy of gastric lesions is at best frequently indeterminate. Therefore, by and large, with carcinoma so common in the stomach and pancreatic heterotopia so uncommon, it would be to the patient's best interest to elect gastric resection. Frequently one of the modifications of the Billroth I operation would be possible and indicated when the lesion is found in the lower third of the stomach. In higher lesions a Polya operation or one of its modifications would be suitable.

In the presence of a diverticulum associated with heterotopic pancreatic tissue, removal of the diverticulum together with the heterotopic tissue is indicated with simple local excision alone or possibly with pyloroplasty or duodenal reconstruction. In the presence of muscular hypertrophy possibly associated with pyloric stenosis, excision and pyloroplasty are indicated.

Whenever pathologic changes are encountered in other organs with the presence of a pancreatic heterotopia and the former seem to have more to do with the patient's symptoms than the latter, the surgeon should not underestimate the potentiality for production of symptoms or actual present clinical significance of the pancreatic heterotopia, complete removal of which should be carried out. The operative procedure advised for pancreatic heterotopia in locations other than the stomach and duodenum is complete but simple extirpation but no generalizations can be made, so varied are the locations. One has to depend on one's surgical judgment in the particular case. As far as the pancreatic heterotopia is concerned, one can be as conservative as possible. In several of our surgical cases of clinically significant pancreatic heterotopia operation had been performed for some other condition prior to admission of the patient to the Mayo Clinic and at a time when the heterotopic pancreatic tissue was not clinically significant. If the heterotopic tissue had been removed at this time, the later operation for its removal could have been avoided. Whenever heterotopic pancreatic tissue is found in the stomach or duodenum incidentally, during the course of an operation

for some other surgical lesion, its excision is indicated to avoid future trouble unless the risk of the procedure outweighs the advantages of removal. A jejunal pancreatic heterotopia, found incidentally during the course of an operation for some other condition, may be left undisturbed with a fair chance that no complications will be observed subsequently unless such pathologic changes are present that there is a question as to either its present or its future clinical significance. The same general rule as the aforementioned one would hold true for pancreatic heterotopia in other locations, although surgical judgment for the particular location varies.

SUMMARY AND CONCLUSIONS

There are approximately 470 recorded cases of pancreatic heterotopia. Pancreatic heterotopia is observed fairly frequently at routine necropsies. We found an incidence of 1 case of pancreatic heterotopia in approximately every 500 operations in the upper abdominal region. The incidence of pancreatic heterotopia is highest in the fourth, fifth, and sixth decades of life.

The ratio of males to females is almost 3 to 1. The most common location is in the stomach, duodenum, and jejunum, where the incidence is almost 70 per cent. In the majority of the cases the mass of heterotopic pancreatic tissue is single and its diameter usually varies from 1 to 4 centimeters.

The histologic picture of heterotopic pancreatic tissue is frequently the same as that of the pancreas itself. The commonest histologic location of heterotopic pancreatic tissue in our series was the submucosa alone. There frequently is intermuscular infiltration. In the vast majority of the cases there is histologic evidence of acinar function. There is no apparent change in the results of analysis of gastric contents associated with a pancreatic heterotopia.

Hypoglycemia and hyperinsulinism have been observed in association with heterotopic pancreatic tissue presenting both benign and malignant change in its insular portion. If exploration is being carried out in a case of hypoglycemia with definite "Whipple's essential triad" and, after a thorough search, no tumor is found in the pancreas, the surgeon should search for heterotopic pancreatic tissue in its most common locations and also in the unusual sites that are capable of exploration. Both adenomas and adenocarcinomas of islet cell type may be present without clinical evidence of hypoglycemia.

Heterotopic pancreatic tissue presents the same pathologic changes as the pancreas itself. In many cases the ducts are found dilated. Malignant change is more likely to take place in heterotopic pancreatic tissue than in the pancreas proper. Pancreatic heterotopia may be the cause of several types of pathologic changes in the adjacent tissues; namely, fat necrosis, inflammation, ulceration, hemorrhage, necrosis, and formation of a diverticulum.

In a high percentage of surgical cases of pancreatic heterotopia (61 per cent of our cases) the heterotopia is found to be of clinical significance. The location is usually gastric or duodenal. Some of the rare adenocarcinomas of the duodenum may have had their origin in heterotopic pancreatic tissue either in the ampulla of Vater or in the papilla of Santorini. The syndromes presented by a pancreatic heterotopia are generally those of gastric or duodenal ulceration, cholecystic disease, or indeterminate digestive symptoms.

The pathologic diagnosis with frozen section technique at the time of operation is of inestimable value. A mass of heterotopic pancreatic tissue can be mistaken for a malignant growth both roentgenologically and at operation with a consequent unnecessary operation. When the pancreatic heterotopia is clinically significant, its simple excision when feasible is entirely sufficient for complete relief of symptoms. When found incidentally at operation, its removal is indicated in the majority of cases.

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SECONDARY SUTURE OF WAR WOUNDS

A Study of Methods and Results in an Overseas General Hospital

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THE success of the U. S. Army Medical Corps policy of early débridement of wounds without primary suture in preventing serious infection was demonstrated repeatedly during World War II. It was equally well known that secondary healing of such débrided wounds by granulation and epithelization often consumed several months. Painful and disabling cicatrices, osteomyelitis, stiff joints, and muscle atrophy were frequent complications of wounds allowed to heal by second intention. Psychoneurosis developed or aggravated during long hospitalization rendered many soldiers unfit for further combat duty. For the first 2 years after Pearl Harbor the tremendous wastes in man-power and in hospital care resulting from such a slow healing were serious hindrances to the war effort.

The obvious answer to these problems was to effect closure of débrided wounds as early as consistent with safety. In World War I primary suture was practiced sometimes on selected wounds not more than 12 hours old (5). The percentage of successful healing in several series of primarily sutured wounds including a few joint wounds was excellent (from 66 to 94 per cent), but there was also a significant mortality rate. It was concluded as a result of those experiences that the use of the primary suture after débridement should be restricted to "quiet periods" in the fighting when the wounded patient could be kept in one hospital until healing was assured. The decision to close the rest depended largely on the reports from routine culture and smear taken at the *daily* dressing. "Delayed primary" suturing of wounds free from hemolytic streptococci, within the first 5 days, was distinguished from the "secondary suture" of all later closures in which inversion of skin edges and a granulating base had developed. In both delayed primary and secondary closures, a miscellaneous assortment of antiseptics had been previously applied to combat the nearly omnipresent infection. Reported results in small series of cases varied from 66 to 88 per cent of "success" (1, 5). In general the methods of early closure of wounds during World War I seemed either too narrow in selection of cases or too cumbersome in practice to be applicable to large numbers of wounds encountered under average conditions of combat.

Experiences reported from the Republican army in the Spanish Civil War obscured the issue in a sense, for, there, emphasis was placed on the plaster encasement treatment of serious extremity wounds (7). The primary missions of reducing fatality rates and obtaining reasonable healing of fractures despite unfavorable tactical situations were accomplished by this treatment. That better and more rapid healing might be obtained by early closures of such wounds in communication zone hospitals and with the help of modern chemotherapeutic agents was not envisaged at that time.

The use of chemotherapy in conjunction with radical débridement in World War II seemed to change the pathology of war wounds. The majority remained grossly as clean as any other surgical wounds, if infection was not introduced by changing the dressing, at least for a week or 10 days following débridement. In overseas base hospitals, surgeons, guided by this finding, tried secondarily suturing these wounds during this initial period when they were "clean." By 1944 this procedure was being performed routinely during the first 10 days after débridement in many U. S. Army hospitals of the Mediterranean Theater.[1] Results were gratifyingly good. In June 1944, Kirtley and Trabue reported 92.7 per cent

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[1]See Circular letter No. 26, The Surgeon, North African Theater of Operations, United States Army, April 19, 1944.

successful healing in one group of 217 "delayed primary" sutures, and only 3 infected wounds in another group of 30 cases studied in detail. In the latter group 71 individual wounds were sutured 4 to 5 days after wounding. Wilson obtained healing without infection in 85 per cent of 224 wounds secondarily sutured when less than 10 days old. In wounds sutured after 10 days the primary healing rate was reduced to 38 per cent. Wilson's study was based on 305 total wounds in 209 patients. The results in both series are colored somewhat by the fact that compound fracture cases apparently were not included.

The work of British surgeons on this important subject as reported to the Congress of Central Mediterranean Force Army Surgeons, Rome, Italy, February 1945, is of special interest. After a somewhat longer period of participation in the war the British were fully aware of the advantages of early closure of wounds. Their efforts as described at that meeting were being directed toward the improvement of results in such wound handling chiefly by the local use of chemotherapeutic agents. Murray reported that 91 per cent of 500 "flesh" wounds treated locally with a penicillin powder at time of suture "healed successfully" after delayed primary suture[1] in contrast to 75 per cent successful healing in 229 "proflavine treated" wounds. In a paper entitled "Early Closure of Compound Fractures" at the same congress Hendry reported 60 per cent of his cases with complete healing of the skin over major fractures of long bones within 6 weeks after delayed primary suture.

Secondary closure was performed on the wounds of approximately 2200 patients at the 6th General Hospital situated near Rome, Italy, during July, August, and September of 1944. The present report is based chiefly on a series of 1110 of these patients with more than 2700 individual wounds. Most of the balance consisted of a number of patients operated upon during this period which could not be included solely because the press of work at times made it impossible to obtain and record the necessary data. At least 100 patients were evacuated to the rear to create bed space before healing results could be evaluated. Quite a few cases, in which wounds were limited to amputations or to wounds of the fingers, toes, or face, were excluded also because they represented a different sort of surgical problem. Aside from these specific omissions the series was unselected and included various types of soft tissue wounds as well as those associated with compound fractures. Thirty different surgeons, operating on these patients, used their own judgment in carrying out the details of the general policy.

[1]Synonymous with our term "secondary suture."

GENERAL POLICY

A great influx of recent casualties arriving from forward hospitals with wounds already débrided made necessary the adoption of "mass production" methods of surgical management. This consisted principally of a systematic performance of secondary suturing in the early "clean" period within a week or 10 days after débridement.

Guided by our own previous experience and reports from other hospitals, it was the policy to leave the dressings unchanged until the patient's arrival in the operating room. However, a few wounds required preoperative inspection because of unexplained fever, pain, excessive drainage or hemorrhage. In general this method represented a vast saving in time, materials, and discomfort to the patient over the "daily dressing" regimen of World War I. Many patients received sulfadiazine by mouth, and this was often continued for several days after operation. The use of penicillin parenterally was not routine and was usually restricted to severe compound fractures, wounds into joints, and grossly infected wounds. Transfusions of blood and plasma, vitamins and other supportive treatment were used as indicated. Most surgeons preferred a time interval of at least 48 hours between admission and secondary suture to allow for rest and observation.

In the group of cases here studied, 96 per cent were admitted to this hospital in time to be scheduled for secondary closure before the tenth day following their débridement. Occasionally secondary closure was contraindicated by the condition of the patient or his wound. It was soon noted that the clinical appearance of the wound on the fifth or sixth day after

débridement suggested that this was the most favorable time for suturing.

On first inspection of these wounds in the operating room we were surprised at the small percentage which seemed unsuitable for closure because of gross signs of necrosis. In a series of over 300 wounds personally observed by the authors, this was less than 5 per cent, and testified to the excellent results from débridement and chemotherapy usually penicillin at forward hospitals. Culturing of wounds for determination of bacterial flora was impractical as a routine procedure.[1] Wounds containing thin purulent exudate, with, at times, slight reddening of skin at margins and turgidity of tissues proved to be trouble makers. Such wounds were very apt to become septic and break down if sutured in that condition and did much better after preliminary treatment for 24 hours or more with wet dressings, of which the most effective seemed to be penicillin solution (500 or 1000 units to 1 c.c.). Patches of fibrin adherent to otherwise fairly dry and innocent looking wounds usually did not deter healing. A number of wounds, though clean, were of such a large size or so located that they could not be closed completely by secondary suturing. In some, the unsutured part was left to heal spontaneously. In others this area was covered with a split thickness skin graft immediately or at a later date. The longest wound measured 70 centimeters extending from the lateral aspect of the hip to the knee. It healed satisfactorily after secondary suturing. The greatest number of wounds in one patient was one hundred.

TECHNICAL ASPECTS OF SECONDARY SUTURING

Anesthesia. Intravenous sodium pentothal was the most commonly used anesthetic agent. There were no deaths attributable to pentothal in this series. Novocain, locally, was used in about one quarter of the cases. Infiltration of subcutaneous tissue from the wound surface seemed simpler and caused less discomfort to the patient than block anesthesia through the intact skin.

[1]The wisdom of this decision to omit routine wound cultures was confirmed later by the work of Bently and Thomson who found that only 30 per cent of a series of 614 grossly clean wounds contained pathogenic bacteria and that satisfactory healing was obtained after secondary suturing in 62 per cent of even these "infected wounds."

Surgical technique. Accurate approximation of the entire depth of the wound without excessive tension was the primary objective of the operation. It was felt that the less cutting or surgical manipulation of any kind, the less risk there would be of breaking through the natural defenses against infection that had been mobilized about the wound edges in the preceding days. Wounds more than a week old, however, generally require freshening or freeing up of the margins to obtain apposition of the skin edges without inversion. Wounds over large muscle bellies, as in the thigh, buttocks, or arm, often presented a problem in closure unique to war injuries. The swelling of injured muscles at times produces wide retraction of wound margins. Where there is no significant skin loss, the degree of tension required to close these wounds accurately reflects the amount of edema to be reduced. Therefore, marked tension in the closure of these particular wounds is not only tolerated, but proportionately necessary to relieve lymphostasis and congestion, and undermining the edges to avoid this tension in such wounds is undesirable. Where there was major skin loss extensive undercutting was resorted to without hesitation in order to close the wound. Advancement and rotation of contiguous skin flaps occasionally permitted closure of wounds in which even wide undermining did not accomplish this result. Due to experience with flexion deformities and recurrent breakdown of scars which were situated vertically over joints, particularly in the popliteal space, we utilized these maneuvers to obtain more nearly transversely placed suture lines in such areas. Black silk was the most commonly used suture material, employed sometimes in conjunction with silkworm gut. The latter seemed to cause less tissue reaction and "cutting through" when under tension. The deep fascia was approximated as a separate layer in a few cases. Several instances of postoperative wound infection were seen with extrusion of nonabsorbable sutures, however, and therefore buried sutures were avoided as a general policy. If the edges of aponeurosis or fascia are included in the deep bites of vertical mattress sutures, solid healing will be obtained in most cases. Of the few postoperative mus-

cle hernias observed, only an occasional one has been symptomatic.

At first many deep wounds were drained at the time of secondary suture because of potential dead space, retained blood clot or borderline infection. With more experience this was found rarely necessary except in cases of compound fractures of the larger bones. Dependent stab wound drainage employing soft Penrose tubing was found preferable to draining through the suture line. The drains usually were removed within 1 to 4 days.

The wound surfaces were dusted with sulfanilamide powder in some cases but only one of the surgeons felt this was sufficiently valuable to employ it routinely.

Casts or plaster splints were applied in many of the extremity wounds involving soft tissues only. After observing the breakdown of several of the unsplinted wounds near joints we were convinced that this should be practiced more widely.

POSTOPERATIVE MANAGEMENT

It appears to be necessary to retain stitches in a secondarily sutured wound longer than is usually necessary in a primarily sutured wound. In the absence of infection the stitches were generally removed in from 10 to 14 days.

Mobilization of joints and muscle training were practiced as early as tissue reaction permitted, in many cases even before wounds were completely healed. Experience showed that wounds of the lower extremities, however, healed far more promptly if patients were kept off their feet until healing was complete.

RESULTS

Percentage of healing. For purposes of detailed study the healing of these wounds was classified as primary, delayed primary, or secondary. The meaning of "primary" healing is obvious. In certain wounds, localized eversion of skin edges, mild stitch reaction, persistence of the drain sinus, or delayed healing where cruciate incision corners had been brought together, did not represent perfect primary healing. The end-result though delayed a few days hardly differed from that in primary healing, however. We called this "delayed primary" healing. Primary and delayed primary healing together constituted "satisfactory" healing. When definite infection and separation or breakdown of the suture line occurred the result was called "unsatisfactory" in so far as value of the operation of secondary suture was concerned.[1]

Calculated on the above basis the overall healing results in the series were as follows: For 1110 cases the healing was either primary or delayed primary (and therefore "satisfactory") in 937, or 84.4 per cent; in 173, or 15.6 per cent the healing was unsatisfactory. In an unselected group of about half the cases (605 cases) the effect of an associated compound fracture was noted. Serious compound fractures were present in 110 of these. There were incomplete or chip fractures in 20 other cases. In 85, or 77.3 per cent, of the 110 major fractures, the secondary closures healed satisfactorily. Although lower than the "satisfactory" percentage for the total, we feel this is an acceptable showing for the large and complicated wounds of this type. Twenty-three of these involved humerus or femur; 18 of the compound wounds healed "satisfactorily" in this small group, and only 5 were "unsatisfactory." There were no cases of infection or gangrene leading to amputation attributable solely to the closure of the wound, and no deaths. Secondary suturing of wounds complicated by compound fractures, then, was found to be a safe and justifiable procedure.

Optimum time for secondary suture. Table I shows the ratio of satisfactory to unsatisfactory healing after secondary suture by days from date of wounding. The ratio of virtually 10:1 for cases operated upon the 6th day after wounding is the best showing for any of the larger groups. After the 6th day the ratio becomes definitely less favorable. Since the delay in débridement of the wounds averaged nearly 24 hours, the choice of 5 days as the optimum time from débridement to secondary suture appears to be vindicated statistically in this series of cases.

Choice of anesthesia in secondary suture. Local anesthesia was used in 243 cases with satisfactory healing in 215 or 88.4 per cent, unsatisfactory in 28 or 11.6 per cent. General

[1] In all the tables in this report, the figures refer to cases and not to individual wounds. Where there were multiple wounds, if only one broke down, the case was labelled "unsatisfactory."

anesthesia was used in 867 cases with satisfactory results in 722 or 83.3 per cent, unsatisfactory in 145 or 16.7 per cent. Local novocain was used generally in the smaller wounds and only where there was no obvious sepsis. Keeping this method of selection in mind, it is clear that in this series the use of infiltration anesthesia did not increase the postoperative rate of infection or adversely affect the percentage of satisfactory healing. We know of no instance of significant wound infection attributable solely to the use of local anesthesia in the closure.

Disposition. The figures for disposition after secondary suture in this hospital were available for 1204 patients as follows: There was a salvage rate of approximately 72 per cent of the men for General Service within an average time of only 6 weeks after wounding. The disposition of a great majority of the 18.1 per cent discharged for evacuation to the Zone of the Interior (United States) was determined by the presence of fractures, nerve injuries, amputations or other conditions not directly affecting the healing of their wounds. A higher percentage of the Limited Service cases were so reclassified chiefly because of wound disability, but other conditions or complications also dictated this disposition in many cases.

TABLE I.—HEALING RESULTS BY DAYS FROM WOUNDING TO SECONDARY SUTURE—1110 CASES

Interval in days	Total cases	Satisfactory	Unsatisfactory	Ratio	
				Satisf.	Unsatisf.
3	18	18	0	..	..
4	91	80	11	8.2	1
5	174	155	19	8.0	1
6	238	216	22	9.8	1
7	200	173	27	6.4	1
8	163	131	32	4.0	1
9	79	58	21	2.7	1
10	37	24	13	1.8	1
11	35	31	4	7.7	1
12	22	18	4	4.5	1
13	13	8	5	1.6	1
14	12	7	5	1.4	1
15 or more	38	28	10	2.8	1

OBSERVATIONS

We feel that the healing results obtained in this large series of war wounds can be improved with more experience. Limitations as well as possibilities of secondary suture have been learned. Some of the older or slightly infected wounds might have healed better after application of hot compresses or antiseptic dressings for a few days before suturing. The more experienced use of the various plastic surgical maneuvers to obtain approximation of skin edges without tension, more thorough splinting of wounds near joints, and enforced bedrest during healing of leg wounds all should increase the percentage of satisfactory results. As noted above (2), British Army surgeons found that the local application of penicillin to the wounds increased their ratio of successful healing after secondary suture. They did not have a comparable series of wound cases with systemic penicillin treatment but showed that wound infection sometimes developed despite intramuscular penicillin in usual doses. Further reports may clarify this subject.

Secondary suturing may be applied in peace-time traumatic surgery. The majority of such wounds, whether due to vehicle and industrial accidents or injury by firearms, explosives or other means, will prove amenable to immediate primary suture after thorough débridement. In the light of present knowledge the administration of penicillin systemically would be indicated in all but minor wounds. A few wounds with excessive contamination, marked tissue destruction, or prolonged time lag between injury and treatment will be more safely handled, however, by delayed suture. We would suggest culturing a wound of this type at the time of débridement. Sulfanilamide or penicillin[1] could be applied topically, if the surgeon desired, and an occlusive dressing applied. The first change of this dressing should be made in the operating room on the fourth or fifth day. If the wound appeared grossly clean and the first culture had grown no hemolytic streptococcus, secondary suture would be indicated at that time. If, however, the wound appeared septic

[1]Some British Army surgeons favor a penicillin-sulfathiazole powder for this use and frost the wound surface thoroughly.

or the culture revealed hemolytic streptococcus, suture should be deferred for at least 2 days. Wet dressings, perhaps with penicillin solution, should then be applied frequently until the wound becomes sufficiently clean to tolerate suturing. Such a routine should result in satisfactory healing in a very high percentage of cases.

SUMMARY

The results of secondary suturing of a series of wounds at an overseas General Hospital during World War II have been analyzed.

In 937, 84.4 per cent, of 1110 cases, satisfactory healing was obtained as a result of this procedure.

It was found to be safe and generally satisfactory to suture secondarily those wounds associated with compound fractures.

Details of technique and management related to secondary suture are discussed.

It was possible to return 71.9 per cent of the men to general service; 10.0 per cent were reclassified to limited service, and 18.1 per cent were discharged from this hospital for evacuation to the Zone of Interior.

The application of this method of handling to certain peacetime wounds is recommended.

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POSTCAVAL URETER, WITH DESCRIPTION OF A NEW OPERATION FOR ITS CORRECTION

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THE location of the right ureter behind the vena cava, instead of overlying it, is a very rare anomaly; only 33 cases having been reported in medical literature to date. Even rarer is corrective surgical treatment of the condition, only 4 such attempts having been reported previous to the one presented here.[1]

In the present case a new operation was utilized which appears to have merit. It will therefore be described in detail.

REVIEW OF THE LITERATURE

Hochstetter, in 1892, was the first to describe a case of postcaval ureter in man; this was in an infant a few weeks old, and was discovered during routine dissection.

Pick and Anson tabulated 28 cases up to 1940, including one of their own. Five more have been added since, one each by Harbach (1940), Harrill (1941), DeCarlo (1941), Gruenwald and Surks (1943), and Wilson and Herzlich (1944). The author's case makes the thirty-fourth to be reported.[2]

Of these 34 cases, 22 were diagnosed at postmortem examination or laboratory dissection, 11 (including ours) at operation, and only 1 before operation.

All but 3 of the 34 patients were adults. Of these 3 cases, all discovered at routine dissection, one was in a stillborn infant, another in an infant a few weeks old, and the third in a year old child.

Twenty-five were males, 7 were females, and in 2 cases the sex was not given. It has been suggested that the fact that males outnumber females by more than 3 to 1 in the reported cases may be accounted for by the greater number of male bodies that come to the dissection room and the postmortem table (where a majority of these cases were discovered). Of the 11 patients operated upon, 7 were males and 4 females. Although a small group, this would seem to bear out the belief that the anomaly is more common in males.

Postcaval ureter may take several forms. The most common form is unilateral persistence of the posterior cardinal vein (observed on the right side only), the postrenal segment of this vein forming the postcava. Most of the reported cases are of this type. In 5 cases (Rotter, Uebelhoer, Adachi 2, and Harrill) there was double postrenal vena cava, one on the right and one on the left side, the ureter passing behind the corresponding vein. In only 1 case (Gladstone, 1905) was there bilateral involvement. This case, a stillborn acardiac infant, showed bilateral postcaval ureters (double postrenal vena cava, one on each side of the aorta, with each ureter passing behind its respective vein).

EMBRYOLOGICAL CONSIDERATIONS

Present day opinion unanimously ascribes the anomaly to the embryonic vascular system rather than the urinary. Faulty development of the inferior vena cava, and not maldevelopment of the ureter, is the etiological factor responsible. In most of the reported cases the preureteric vena cava was associated with other anomalies of the retroperitoneal veins.

All later attempts at explaining the origin of anomalous retroperitoneal veins are based on the embryological work of McClure and Butler (1925) and Gruenwald (1938). Randall and Campbell, Pick and Anson, and Gruenwald and Surks have gone thoroughly into the embryology of postcaval ureter, and the reader is referred to their papers.

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[1]Commander Moody, of the U.S.N. Hospital at St. Albans, N.Y., has notified the author of a sixth patient operated upon by him recently. He severed the ureter and made an end-to-end anastomosis over the vena cava.

[2]Since this article was submitted, an additional case has been reported by Doctors L. F. Greene and W. M. Kearns of the Mayo Clinic. This was the second case in which the diagnosis was made before operation and the fifth case in which plastic repair was done. The ureter was severed and anastomosed in its upper portion.

Briefly, in the development of the embryo three bilaterally symmetrical pairs of veins appear in the lumbar region: the posterior cardinals (lateral), the subcardinals (ventral), and the supracardinals (dorsal). Numerous anastomoses between these form venous rings.

Quoting from Pick and Anson:

"During fetal life the permanent kidney (metanephros), having developed in the pelvis, ascends to the upper lumbar level, passing through a ring of venous channels (perimetanephric or periureteral ring). The ventral limb of the ring is formed by the lumbar division of the postcardinal vein and the subcardino-postcardinal anastomosis (McClure and Butler; and sacrocardinal vein according to Gruenwald). The dorsal limb is a derivative of the lumbar division of the supracardinal vein and the subcardino-supracardinal anastomosis (McClure and Butler: or sacrocardinal vein of Gruenwald).

"Normally the postrenal portion of the inferior vena cava arises from the dorsal limb of the perimetanephric ring, the ureter thereby being placed in an antecaval position. But, in the anomalous arrangement of the ureter and vessel, one of the following developmental alterations occurs: (1) the ventral, rather than the dorsal, limb persists, the ureter then being postcaval, (2) the dorsal limb fails to arise at all—with similar results, (3) both limbs are present and persistent—the ureter passing between cavae."

Most writers on the genesis of this anomaly agree that it forms from that limb of the embryonic perimetanephric ring which normally degenerates, that is, according to McClure and Butler, the cardinal vein. However, two later writers (Gruenwald and Surks), after going very extensively into the embryology, express the opinion that the preureteric vena cava is a derivative of the subcardinal rather than the cardinal vein.

SYMPTOMATOLOGY

Symptoms, when present, are those of ureteral obstruction. The condition may be present throughout life, however, without causing symptoms.

Examination of most of the kidneys in adults showed hydroureter and, in varying degrees, hydronephrosis and pyonephrosis. Stone formation was an occasional accompaniment. None of the 3 cases in infants showed evidence of obstruction.

Hydronephrosis may be produced by pressure exerted by the vena cava upon the underlying ureter, or by kinking or stricture due to the anomalous course of the duct. Uebelhoer states that in certain cases the constriction may be due to the right ovarian vein crossing the postcaval ureter.

In our own case the symptomatology consisted of dull backache high up between the shoulder blades, of 3 weeks' duration, accompanied by hematuria on two occasions, severe headache at night, and intermittent burning on urination.

DIAGNOSIS

In only 1 of the reported cases (Harrill's) was the diagnosis made preoperatively—a not extraordinary fact, perhaps, when one considers the extreme rarity of the anomaly. Cognizance on the part of the examiner that the condition may exist would appear to be a most important factor in preoperative diagnosis, since the x-ray findings are quite distinctive.

In Harrill's case the clinical picture was that of obstruction. Bilateral stereoscopic pyeloureterograms revealed a hydronephrotic right kidney with an elongated pelvis. From the ureteropelvic junction the ureter curved upward in a wide arc toward the midline, then downward toward the right side, after which it continued downward in a normal course. As an important aid in diagnosis this author suggests a complete series of stereoscopic roentgenograms taken in the anterior, posterior, and oblique positions. He states: "When viewed stereoscopically the radius of curvature should be great enough to include a structure having the diameter and position of the vena cava."

Another distinctive x-ray finding that has been pointed out is the peculiar position that the ureter bears to the spinal column when lateral films are taken. In an oblique roentgenogram, that portion of the ureter which courses dorsal to the vena cava will be found to impinge against the lower lumbar spine, while the normally situated ureter will fall away from it.

In the postcavally placed ureter, the displacement is always toward, to, or even beyond the midline of the body. The duct, winding around the vessel, forms a sickle-

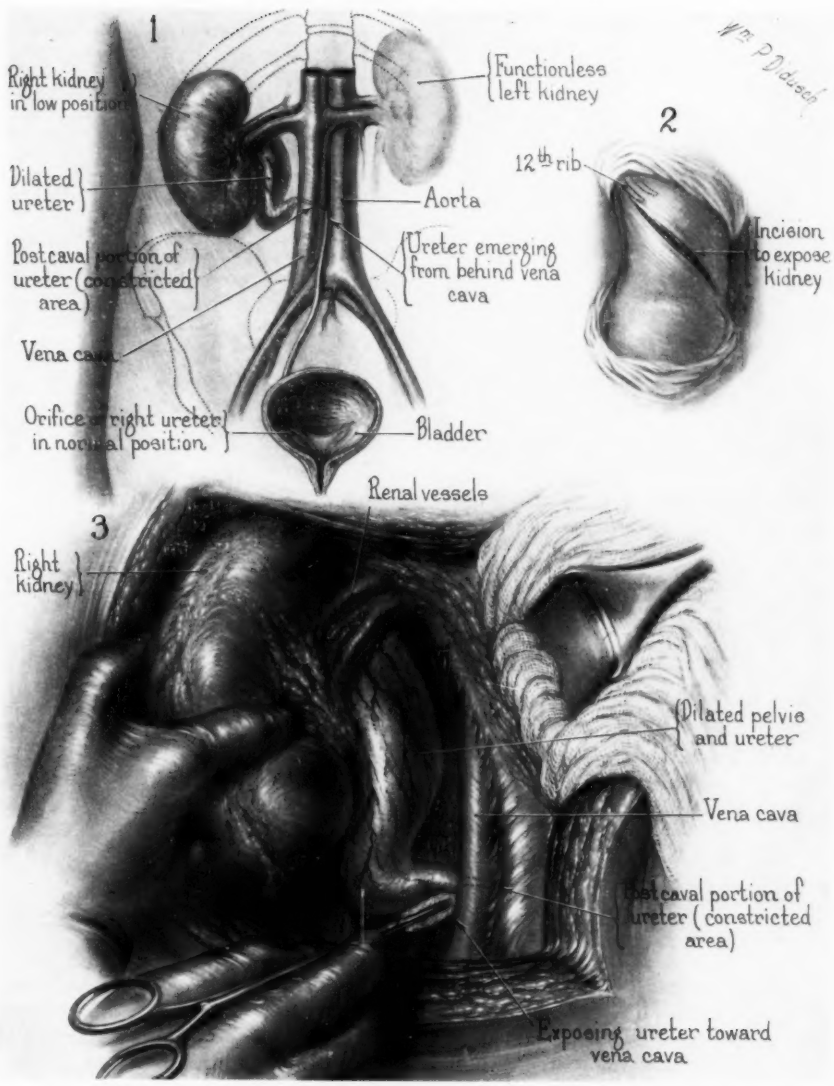

Fig. 1. 1, Condition before operation. Right kidney in low position; ureter passes behind vena cava, and this portion of ureter is constricted. Left kidney is functionless. 2, Incision to expose right kidney and upper part of ureter. 3, Kidney exposed. Upper part of ureter and renal pelvis greatly dilated. Ureter being freed toward vena cava at point where it passes under the vein. Ureter constricted at this point (indicated by dotted line).

shaped curve with the convexity directed supermedially. The roentgenograms in our case showed the right ureter to be very near the midline of the spinal column. This patient had a left kidney shadow and a left ureteral orifice in the bladder, but the ureter could not

be catheterized nor was there any evidence of shadow-casting material in this region in the intravenous urogram.

In most of the reported cases, in which operation was done, the clinical picture was that of ureteral obstruction with the cause of the obstruction remaining obscure. It is our opinion that postcaval ureter should be considered in all cases of hydronephrosis of obscure etiology, especially when the roentgenograms show a double right-angled kink with the ureter below this point displaced toward the midline.

TREATMENT

Corrective surgery—namely, transference of the ureter from its anomalous position behind the vena cava to a more nearly normal site—is the procedure of choice. In some cases, however, the kidney will be found so badly damaged that nephrectomy becomes necessary.

A review of the 11 cases in the literature in which operation was done discloses that nephrectomy was performed in 6, nephrolithotomy alone in 1, and corrective procedures in 4 (Kimbrough, 1932; Uebelhoer, 1936; May, 1938; Harrill, 1940). In all 4 cases the ureter was divided, disengaged from the retroperitoneal tissues, drawn from behind the vena cava, placed in normal position, and anastomosed. Harrill's was the only case in which the division and anastomosis were above the ureteropelvic junction. The results in all 4 cases were reported as good.

In our own case, because it was deemed advisable to preserve the intrinsic nerve supply, the ureter was severed at its point of entry into the bladder wall, removed from behind the vena cava and placed in normal position, and its end reimplanted in the bladder wall as described below.

REPORT OF CASE, WITH DESCRIPTION OF NEW OPERATION

L. P. a white male, aged 44 years, was admitted to the Department of Urology (James Buchanan Brady Foundation) of the New York Hospital on April 19, 1945, complaining of pain between the shoulder blades, of 3 weeks' duration, with severe headache at night, hematuria on 2 occasions, and intermittent burning on urination.

The past history was unimportant.

The right kidney could be felt on palpation. The urine showed 10 per cent pus and an occasional red blood cell; the prostatic secretion showed 20 per cent pus. Otherwise the physical examination, including rectal examination, was essentially negative.

A complete urological investigation was done. Cystoscopy revealed trabeculation in the region of the left ureteral orifice and considerable edema of the vesical orifice. A lead catheter No. 6-F passed to the kidney pelvis on the right side, but a No. 4-F catheter could be passed only about 5 centimeters on the left side. The x-ray films showed a small kidney shadow, high in position, on the left side, and a kidney shadow, large in size and low in position, on the right side. There was a large moth-eaten shadow opposite the transverse process of the third and fourth lumbar vertebrae and another just opposite the fifth lumbar vertebra: these were thought to be calcified lymph glands. The right pyeloureterogram showed a greatly dilated kidney pelvis and a right-angled kink of the ureter. None of the shadow-casting material entered the left side. Excretory urograms at 5, 10, and 25 minutes were made. These showed prompt function on the right side and no evidence of function on the left.

The impression was that the patient had a dead left kidney and a right hydronephrosis with a kink of the ureter.

Two days after admission, the right kidney was exposed under spinal anesthesia.

OPERATION

With the patient lying on his left side and on an elevator to put the right loin on a stretch, the usual lumbar incision was made from the costovertebral angle downward and forward to below the twelfth costal margin. This was deepened through the subcutaneous fat, fascia, and muscular layers.

The kidney was exposed and isolated, as was the ureter. The latter, which was greatly dilated, was followed for a distance of about 12 centimeters below the ureteropelvic junction, where it was found to pass under the vena cava, the dilatation being above the point where the ureter passed under the vessel.

The mobilized kidney was incised and a drainage tube (No. 24-F Malecot four-winged catheter) was inserted into the dilated pelvis and fixed in place with ribbon gut, with a pad of fat which caused perfect stasis of blood. The kidney was then fixed in position by means of two ribbon-gut sutures inserted into Gerota's fascia and the quadratus lumborum muscle, forming a shelf for its support. The upper portion of the wound was partly closed.

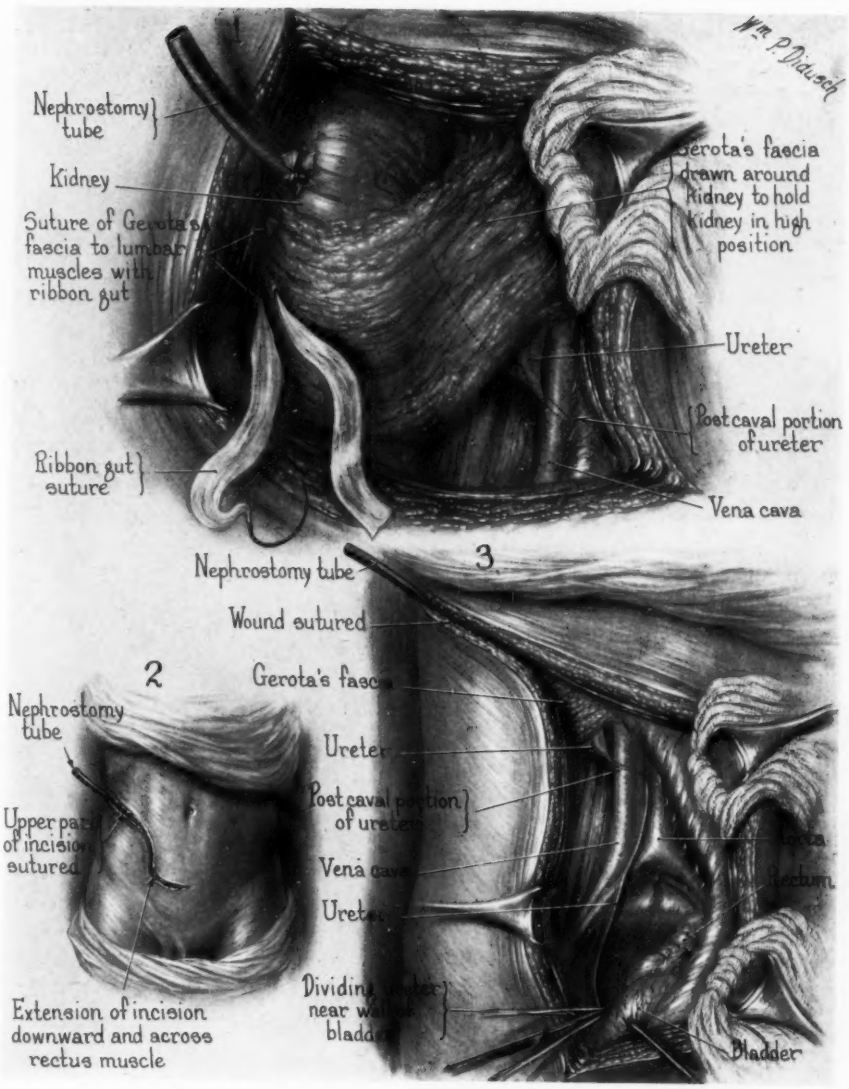

Fig. 2. 1, A nephrostomy tube has been placed in the kidney pelvis and fixed in position by ribbon gut. Nephropexy is being carried out by drawing Gerota's fascia around the kidney and suturing it to the quadratus lumborum muscle with ribbon gut. 2, Upper portion of wound partly closed. Incision extended downward and across rectus muscle to expose middle and lower portion of ureter. 3, Entire ureter has been exposed. Dividing ureter close to its insertion in bladder.

The patient was then placed on his back and the lower end of the wound extended down the right border of the rectus muscle and across its lower end to the midline. The incision was deepened to but not into the peritoneum, which was bluntly dissected free and

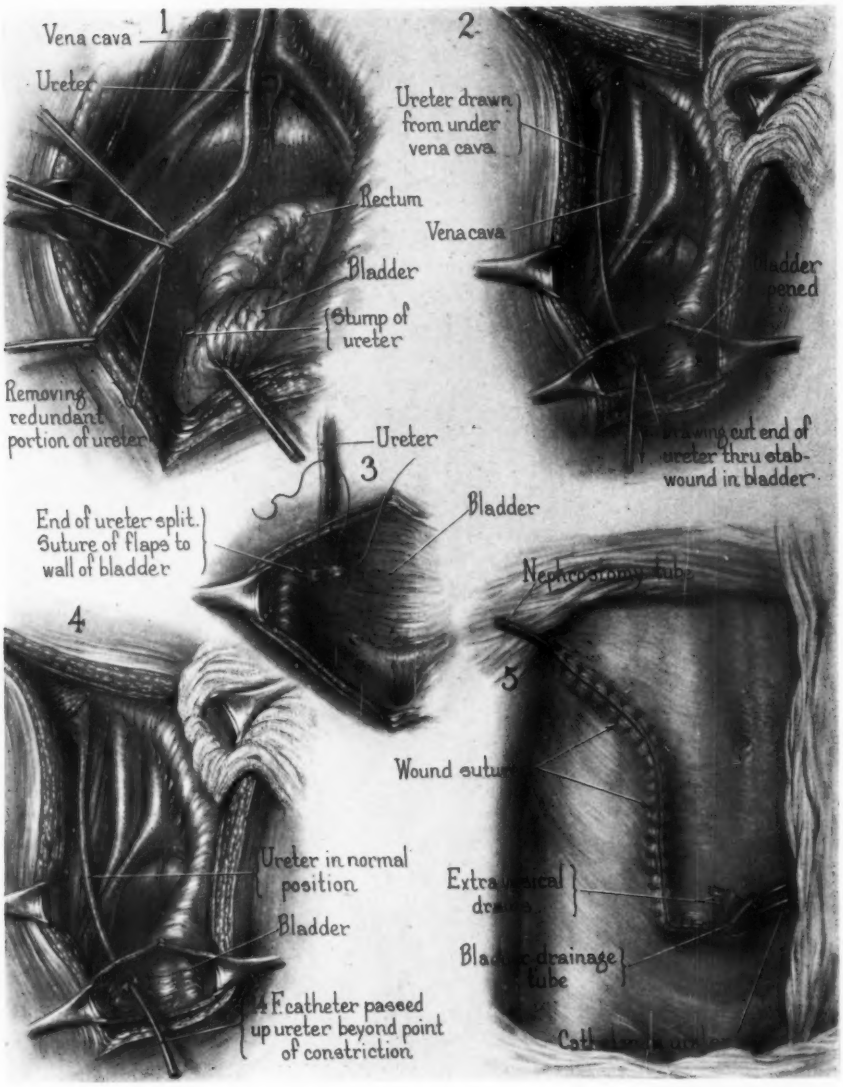

Fig. 3. 1, Removing redundant portion of ureter. 2, Ureter has been drawn from under vena cava; cut end being drawn through stab wound in bladder. 3, Cut end of ureter has been split; flaps being sutured to bladder wall. 4, Ureter reimplanted in bladder. No. 14-F catheter passed up ureter beyond point of constriction. 5, Entire wound has been closed. A drainage tube has been placed in the bladder, and two extravesical drains down to the site of implantation of the ureter. No. 14-F catheter from ureter shown emerging with other drains.

the vena cava exposed. The ureter was identified to it, under it, and passing down mesially across the left iliac vein just before it joined the right iliac to form the vena cava.

The entire lower end of the ureter was isolated, and because it was thought advis-

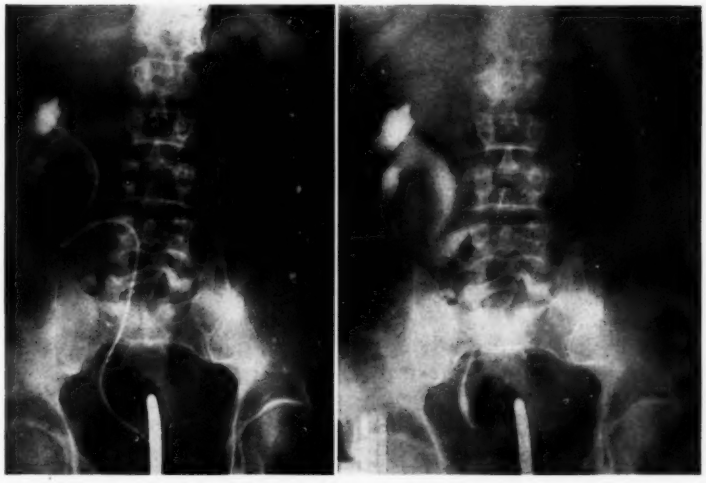

Fig. 4. Pyelogram and pyeloureterogram after the injection of 25 cubic centimeters of skiodan.

able to preserve the intrinsic nerve supply of the ureter, it was tied off at its insertion into the bladder wall. The ureter was then drawn from beneath the vena cava and brought over the vein; the bladder was opened, and the ureter reimplanted into its superior-posterior wall and fixed in position with a chromic catgut No. 00 suture, about 6 centimeters of the lower end of the ureter being excised to allow it to be straight, without tension.

A No. 14-F splinting soft rubber catheter was inserted into the ureter beyond its narrowed point and brought out through the bladder incision and fixed to the skin of the lower end of the wound. A double suction tube was inserted into the bladder, which was closed and the tube attached to the fascia in the lower angle of the wound. Four grams of sulfanilamide were distributed throughout the wound. A drain was inserted to the opening in the bladder and another drain to the anastomosis of the ureter and the bladder.

The wound was closed in layers and the patient returned to his room in good condition.

Postoperative course. After the removal of the splinting catheter, the nephrostomy wound continued to drain. Attempts to insert a catheter by means of the cystoscope were unavailing, and 6 weeks after the first operation it was decided that the patient should again be operated upon.

The bladder was exposed by a Pfannensteil incision extended upward on the right side. It was opened and a No. 10-F catheter was finally passed into the reimplanted ureter after incising the ureter about 3 centimeters above the bladder implantation, at which point there was found to be a tight stricture. The catheter was inserted into the kidney pelvis and out through the urethra, and fixed in position. The ureter was closed by 3 interrupted mattress sutures of No. 0000 catgut. The wound was closed in layers without a drainage tube in the bladder, and the patient was returned to his room in good condition. The No. 10-F ureteral catheter thus passed from the kidney pelvis through the bladder and the urethra.

Subsequently, a discharging sinus required still another operation, at which time it was found that an abscess had developed about the lower end of the ureter and a considerable portion of the duct had sloughed off. The lower end of the ureter was, therefore, implanted into the skin.

The patient has made an uneventful recovery from this final operation. The catheter

passes to a bag strapped to his leg and he goes about his work handling this apparatus very well indeed.

SUMMARY

1. Postcaval ureter is a very rare anomaly, the present case being the thirty-fourth to be reported in medical literature.

2. This is an anomaly of the embryonic vascular system rather than the urinary, being due to faulty development of the inferior vena cava. The preureteric vena cava is usually associated with other anomalies of the retroperitoneal veins.

3. Of the 34 reported cases, 22 were discovered at postmortem examination or laboratory dissection, 11 (including ours) at operation, and only 1 preoperatively.

4. Postcaval ureter may be present throughout life without producing symptoms. Symptoms, when present, are those of ureteral obstruction, which may be produced by pressure exerted by the vena cava upon the underlying ureter, or by kinking or stricture due to the anomalous course of the ureter.

5. Stereoscopic roentgenograms taken in the anterior, posterior, and oblique positions aid in the diagnosis. The x-ray appearances are distinctive in the following respects: (1) In an oblique film the portion of the ureter dorsal to the vena cava will impinge against the lower lumbar spine, whereas the normally situated ureter will fall away from it. (2) The postcavally placed ureter is always displaced toward, to, or even beyond the midline of the body. The ureter, winding around the vessel, forms a sickle-shaped curve with the convexity directed supermedially.

6. Severe damage to the kidney may require nephrectomy. Otherwise, corrective surgery—namely, transference of the ureter from behind the vena cava to its normal position in front of the vessel—is the treatment of choice.

7. Only 4 cases treated by corrective surgery have been reported previous to our own. In 3 of these the ureter was divided and anastomosed in its upper portion; in 1 the division and anastomosis were above the ureteropelvic junction.

8. The operation described here aims at the preservation of the ureter's intrinsic nerve supply while correcting the anomaly. The ureter is severed at its point of entry into the bladder wall, removed from behind the vena cava, placed in normal position, and its end reimplanted into the bladder wall.

CONCLUSIONS

1. Postcaval ureter should be considered in all cases of hydronephrosis of obscure etiology, particularly when the roentgenograms show a double right-angled kink with the ureter below this point displaced toward the midline.

2. Division of the ureter at its vesical end and reimplantation into the bladder wall is preferable to division and anastomosis higher up because (1) the peristaltic wave is not interfered with, and (2) stricture at the site of repair is less likely to occur.

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TOPICAL PENICILLIN TREATMENT OF ESTABLISHED INFECTION IN COMPOUND FRACTURE WOUNDS

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REPORTS concerning the use of parenteral and local penicillin therapy in the treatment of established suppurative infections in compound fracture wounds have been generally pessimistic. The poor results with parenteral therapy are explained by the failure of all but a small proportion of the administered penicillin to permeate the edematous indurated zone of tissue which forms a wall about the site of infection. The principal advantage of local therapy is the high concentration of penicillin which is maintained at the site of infection. The chief objection to this method has been the difficulty of instilling the penicillin solution at frequent enough intervals and with sufficiently sterile technique to obtain the maximum benefits. The purpose of this report is to describe a method of topical penicillin therapy which overcomes these difficulties and which has proved itself to be highly effective in a group of cases which had been refractory to previous treatment by other methods.

The cases in which this method was used were of compound fracture wounds in which established infection had existed for periods ranging from 2½ to 27 months before starting the method to be described, in which penicillin jelly, a mixture of penicillin with lubricating jelly, is applied to the surface of the wound. For the most part, the wounds were produced by shrapnel, machine gun fire, and rifle fire, with resulting extensive destruction of soft tissue and bone. All of these cases had been refractory or had shown little progress with previous treatment, and have shown a greatly increased rate of healing with the change to topical application of penicillin jelly. In some instances this response has been spectacular, healing taking place within a few weeks in wounds which were resistant to other methods of treatment for a period of months.

The average time between wounding and the start of penicillin jelly treatment in the 28 patients comprising this series was 10.34 months. The average time between the initiation of penicillin jelly therapy and complete healing in 23 of the 28 patients was 1.16 months. There were two failures with the penicillin jelly treatment in the sense that the soft tissue wounds failed to heal completely. Three patients remain unhealed at the time of this report, but their progress indicates that healing will be complete within a reasonable period without changing the type of therapy. These wounds had existed for an average period of 16 months prior to penicillin jelly treatment, and showed satisfactory progress but incomplete healing after an average period of 4 months of this therapy.[1]

RATIONALE OF TOPICAL PENICILLIN THERAPY

The pathologic process at work in old compound fracture wounds is a vicious circle in which localized infection of bone usually goes on to sequestration. The infected bone and the sequestra act as local sources for further infection of bone and surrounding soft tissues, which in turn causes further degeneration and sequestration. The cycle will continue as long as sequestra are present or suppuration persists.

The aim of the penicillin treatment is to break up the vicious circle by eliminating or minimizing the infection in the wound while awaiting sequestration, and to arrest infection after sequestra are eliminated. The penicillin mixture to be described, when retained in surface contact with the suppurating area in sufficiently high concentration, acts as a strong deterrent to infection, and when used in conjunction with adequate drainage, elimination of sequestra, aseptic technique, and general supportive measures has proved to be

[1]Observation of these patients was interrupted by the transfer of the author to another hospital.

a b

Fig. 1. Case 22. a, Appearance of tibia, June 12, 1944. A large fragment of devitalized bone was left *in situ* because of the possibility of its regeneration. b, Appearance of the tibia August 10, 1945. The degenerated fragment now shows definite evidence of regeneration, with callus bridging the former gap between the fragment and the shaft of the tibia.

far more effective in promoting healing than has any other method previously used by us in this type of disease.

TECHNIQUE OF TOPICAL APPLICATION OF PENICILLIN

A mixture of penicillin and lubricating jelly in the proportion of 1000 units per cubic centimeter is applied directly to the wound at each dressing, the standard United States Army lubricating jelly containing phenylmercuric acetate 1:6000, glycerite of tragacanth, quince seed and aromatics being used.[1] This vehicle, which is water soluble, releases penicillin more readily than would an ointment base, and its consistency assures its contact with the wound for several days. The acidity of the lubricating jelly, which is in the vicinity of *p*H 4.4, apparently does not inhibit the action of the penicillin. The penicillin jelly is prepared by mixing 1 cubic centimeter of normal saline solution containing 20,000 units of penicillin with 19 cubic centimeters of autoclaved lubricating jelly in a sterile medicine glass. This mixture is prepared just before beginning the wound dressings and is usually sufficient for 6 to 8 dressings. The wound is cleansed with hydrogen peroxide, followed by normal saline solution, immediately preceding the application of the penicillin jelly. Hydrogen peroxide appears to be a valuable adjunct in the treatment and there is no evidence that it lessens the effectiveness of the penicillin when it is used in this manner. Normal saline solution was used alone in some of the earlier treatments and the results were less satisfactory.

Lubricating jelly is in itself a bacteriostatic agent and probably enhances the value of penicillin. An opportunity to compare the effects of penicillin jelly and lubricating jelly without penicillin was afforded in a patient

[1]The preparations of lubricating jelly on the general market should be tested for *p*H and for possible inhibiting action on penicillin before they are used as described here.

c d

Fig. 1. c, Filling of wound defect by blood clot. The clot was injected with penicillin solution and was overlaid with penicillin jelly to prevent infection and thus encourage organization. d, Final wound healing following split-thickness skin grafting of the surface of the organized blood clot.

with wounds on the medial and lateral aspects of the leg. Penicillin jelly was used on the severe medial wound, and the standard lubricating jelly was used on the relatively minor lateral wound. After 2 weeks of treatment the medial wound was completely healed, while the lateral wound showed only moderate improvement. This and other observations offered convincing evidence that the beneficial effects of penicillin jelly are not due to lubricating jelly alone.

Dressings were made at intervals varying from daily to every fifth day during the experimental phase. In most instances there was evidence of bacterial growth if the dressing interval extended beyond the third day. The most favorable response was with dressings daily or every other day, and since the wounds did just as well with dressings every other day that interval is now used routinely. The only exception is in the first few days of the treatment when suppuration is profuse. At that time it is well to apply the penicillin mixture daily, its efficacy being lessened by the mixture with pus. After several days, often within 2 days, the wound becomes so dry that the gauze dressing is found to be fixed firmly to the wound at each dressing. This adherence is due to the drying action of the lubricating jelly and to the lessened purulent secretion.

Strict surgical technique is observed in performing the dressing. This is especially important in a large ward with a variety of septic wounds where cross-infection with organisms of high virulence is a constant danger. The dressers wear caps, face masks, and gowns; the patient's mouth is away from the wound, and the dressings are done in a private room whenever possible in order to avoid the dust of the ward. Casts are changed if they become soiled with exudate. Instrument technique is used throughout.

Treatment with penicillin jelly has distinct advantages over the method of instillation of penicillin solution through tubes. The latter

a b c

Fig. 2. Case 20. a, Perforating wound of lower third of femur with depression due to loss of soft tissue and bone. b, Appearance of soft tissue wound 20 months after wounding. Exposed bone is partially covered with suppurating granulation tissue. c, Treatment of the wound with penicillin jelly for 27 days followed by split-thickness skin grafting of exposed bone surface has resulted in complete healing.

method was used in earlier cases, but was discontinued because of the difficulties encountered in administering the treatment. The chief objection was that the instillations were often made by unskilled personnel, and it was impossible to prevent micro-organisms from entering the wounds through the tubes due to errors in handling syringes and in managing the ends of the tubes. Three of 10 wounds thus treated became contaminated with bacillus pyocyaneus within a period of 2 days. Another objection was the work entailed in making the instillations at intervals of 3 hours in a large number of cases.

BACTERIOLOGY

Bacteriological studies were made to determine the organisms present in the wounds and to determine the resistance of the infecting bacteria to various concentrations of penicillin. The finding of especial interest was the tendency of organisms which persisted in the wounds to show a progressively increasing resistance to the action of penicillin. This was particularly noticeable with Bacillus proteus. With the beginning of treatment several wounds showed cultures of Bacillus proteus which were completely inhibited by concentrations of penicillin as low as 25 units per cubic centimeter. Cultures taken after 2 weeks showed Bacillus proteus from the same wounds to be completely resistant to concentrations of 1000 units per cubic centimeter. For the most part, Bacillus proteus was resistant from the beginning to concentrations of 250 units per cubic centimeter or higher. This was also the case with Bacillus pyocyaneus. Staphylococcus was susceptible to low concentrations of penicillin in most instances. Twelve cultures showed complete inhibition with 25 units or less, 1 was susceptible to 100 units, and 1 to 250 units. There was little opportunity to check variations of susceptibility in this organism during penicillin therapy as the staphylococcus usually disappeared after a few days of treatment. Organisms which showed complete resistance to concentrations of 1000 units of penicillin per cubic centimeter, including Bacillus proteus and Bacillus pyocyaneus, did not prove to be troublesome contaminants, and usually disappeared from the wounds within a few

weeks. There has been an unusually high incidence of Bacillus proteus in this group of patients. This may be explained by the fact that a majority were previously treated with penicillin intramuscularly or with sulfonamides, and the resistant proteus bacillus remained in the wounds after other organisms had been made to disappear.

Suppuration has been controlled in all of the wounds treated by this method, regardless of types of bacteria present, so it is not considered essential to make detailed bacteriological studies except for investigation purposes.

CLINICAL AND PATHOLCGICAL FEATURES CF WOUNDS TREATED

The 28 cases of compound fractures with long standing wound infection which comprise this series had been refractory or were slow in response to treatment by other methods before beginning the treatment with penicillin jelly. Wounds of short duration and wounds which were near completion of healing when the penicillin jelly treatment was started are not included in this report. The injuries treated involved the following bones:

	No. cases
Tibia, or tibia and fibula	16
Tarsal and metatarsal bones	5
Femur, including hip joint	3
Shoulder joint, involving head of humerus	2
Shaft of humerus	1
Sacrum, complicated by pelvic abscess	1

The local pathologic changes which were considered most significant in influencing the course of the disease were suppurative cellulitis, edema of varying degree, localized degeneration and necrosis of bone with or without sequestration, degeneration and necrosis of the soft tissues, and impairment of regional circulation due to direct injury, edema, thrombosis and trophic changes. In addition, there are to be considered the variables of the injuring force, and the depth and irregularity of the wounds. As stated previously, the types of bacteria did not appear appreciably to influence the course of the healing.

INFLUENCE OF BONE SEQUESTRATION ON WOUND HEALING

The course of wound healing was influenced as much by the proper removal of sequestra as by any other factor. Removal of large sequestrated fragments was delayed as long as there appeared to remain a possibility of revascularization. This has caused a delay in healing in some cases because of the eventual complete necrosis of the fragment, but the value of the segment, if it did revascularize, more than compensated for the delay in healing time. The following case illustrates this point.

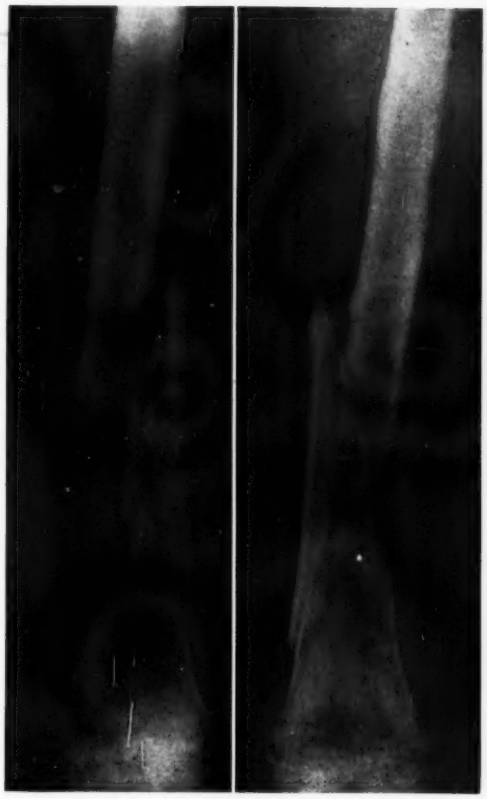

Fig. 3. Case 21. a, left, Appearance of femur 7 months after refracture. An intractable draining wound persisted throughout this period, and was thought to be responsible for lack of tendency to union. b, Secondary closure following 31 days of penicillin jelly treatment resulted in permanent healing of the soft tissue wound and union of the fractured femur.

CASE 22. Revascularization of devitalized bone segment (Fig. 1).

Patient, aged 30 years, was wounded in combat by shrapnel early in February, 1944, sustaining a severe

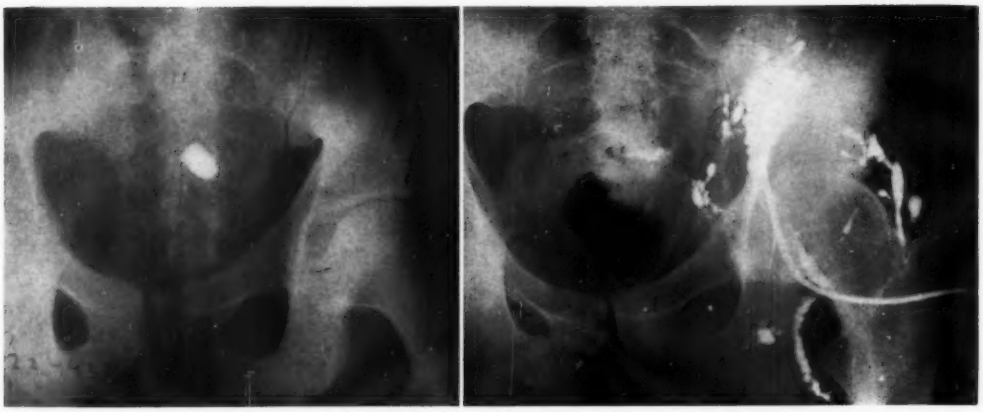

Fig. 4. Case 28. a, left, Perforating fracture of sacrum with bullet lodged in pelvis. Multiple operations for drainage over a period of 13 months, and removal of the bullet, were unsuccessful in arresting suppurative infection in pelvis. b, Injection of sinus tract, originating in the pelvis and emerging over the left greater trochanter, with contrast medium shows the principal pocket in the left iliac region within the pelvis. The abscess, which had persisted for 20 months, became healed after 14 days of treatment with penicillin jelly injected into the tract every other day. Observation for 6 months following healing shows no evidence of recurrence of infection.

compound comminuted fracture of the middle third of the tibia. Early treatment included débridement, sulfadiazine orally, and closed cast which was continued until June 12, 1944, at which time it was decided not to remove a large devitalized segment of cortical bone because of the certainty of weakening the tibia by its removal.

The wound was then treated for several months with various topical medications including sulfathiazole ointment, azochloramide solution, and aqueous solution of penicillin in the strength of 1000 units per cubic centimeter. The wound remained indolent with little roentgenological evidence of bone regeneration in the devitalized segment of tibia.

Penicillin jelly treatment was instituted December 11, 1944, following which there was prompt epithelization of the wound together with evidence of progressive regeneration in the devitalized bone and union of the fracture.

Small spicules of sequestrated bone became detached from the regenerating cortical fragment from time to time, and operation was performed on March 14, 1945, for removal of devitalized bone from the surface of the fragment. The wound defect was allowed to fill with blood. It was not possible to close the soft tissues over the defect. The blood clot which formed was treated with injections of several drops of penicillin in normal saline solution, 1000 units per cubic centimeter, on the first, third, and fifth days following operation. Intramuscular injections of penicillin, 20,000 units every 3 hours, were given for a period of 15 days beginning 2 days before operation. The blood clot was covered with penicillin jelly.

The clot became organized in 3 weeks and was then covered with split-thickness skin grafts. Surface healing was complete on April 30, 1945. Later x-ray examinations showed satisfactory union of the revascularized segment with the shaft of the tibia.

The importance of carefully planning the operation of sequestrectomy cannot be overemphasized. The sequestrum should be accurately localized beforehand by roentgenographic study with views in addition to the standard anteroposterior and lateral whenever necessary. The incision is planned to permit a direct approach to the necrosed bone with a minimum of disturbance to living bone and soft tissues. In some of our patients it was necessary to make the incision through normal skin away from the wound to accomplish this. In 2 instances in this series, wound healing was unnecessarily delayed because of failure to remove all of the sequestra present. In these cases, the operative incisions were inadequate for proper exposure of the diseased area.

All operations of sequestrectomy as well as other types of revision operations are preceded and followed by several days of intramuscular penicillin therapy.

The particular advantage of topical treatment with penicillin jelly in wounds harboring sequestra is that further necrosis of soft tissue and bone is held in check by the inhibiting effect of the penicillin on the infection, thu-

breaking the vicious circle described previously.

PRESENCE OF DEGENERATED BONE

The difficulties of management of degenerated bone are much the same as with sequestra. Degenerated bone causes greater delay than does sequestrated bone because it is impossible in most instances to determine whether the degenerated bone will revascularize or will go on to necrosis. Extensive loss of bone makes it necessary to conserve as much osseous tissue as possible, therefore one must guard against sacrificing bone in which there remains any possibility of revascularization. The point is stressed that, although early healing is desirable, it is not so important that it should be attained through the sacrifice of valuable fragments.

EXCAVATED WOUNDS

Depressed wounds due to loss of bone substance, especially those in which bone remains exposed, are definitely a cause of delayed healing. This is noteworthy in shoulder wounds with partial or complete loss of the head of the humerus in which the wound is held open by the surrounding bony prominences. Two such cases, in which healing was making little progress with sulfathiazole ointment, azochloramide instillations and penicillin instillations used successively, showed a remarkably rapid response to penicillin jelly.

CASE 25. Healing of shoulder defect.

Patient, aged 20 years, was wounded in action on June 24, 1944, sustaining a mortar shell injury with a severe compound fracture-dislocation of the head and neck of the left humerus, together with other injuries.

The wound was débrided and an Orr dressing in shoulder spica cast was applied. He was evacuated to the United States after several months, arriving at this hospital September 5, 1944. Removal of the cast several days after his arrival here revealed a deep cone-shaped wound on the prominence of the shoulder, measuring 5 centimeters in diameter and 6 centimeters in depth.

Closed cast treatment was continued until October 18, 1944, after which time the wound was dressed through a fenestration with hydrogen peroxide cleansing and 5 per cent sulfathiazole ointment. Healing progressed slowly, and on November 16 the local therapy was changed to instillations of aqueous solution of penicillin, 500 units per cubic centimeter, through a small caliber soft rubber tube every 4 hours. Some improvement was noted with this change in treatment, but the method was cumbersome and there was evidence of wound contamination, apparently due to faulty technique in making the instillations.

Penicillin jelly treatment was started December 11, 1944. Improvement was noticed within a few days, and the wound, which had remained almost stationary at 2 centimeters in diameter and 3 centimeters in depth for some weeks previous to the use of penicillin jelly, now healed rapidly, and was completely closed on January 30, 1945.

Arthrodesis of the shoulder was performed on April 12, 1945, with primary healing of the surgical wound.

Healing by organization of blood clot was accomplished in 4 cases of tibial defect. Blood was permitted to fill the defect following sequestrectomy and saucerization of the bone. The resulting blood clot was injected with a few drops of a solution of 1000 units of penicillin per cubic centimeter of normal saline solution. The surface of the clot was protected by a dressing of penicillin jelly. Wounds treated in this manner showed gross evidence of organization of the blood clot 3 to 4 weeks after operation. In 2 instances, the organizing clot was overlaid with split-thickness skin grafts 4 weeks after operation. None of the clots liquefied or became infected, and there was only slight depression of the area on completion of healing. In the light of previous experience with organization of exposed blood clot, it is reasonable to assume that penicillin played an important rôle in the healing in these cases (Fig. 1, c and d).

CASE 14. Healing by organization of blood clot.

Patient, aged 27 years, was injured by shrapnel in combat with the enemy October 26, 1944, sustaining a severe compound comminuted fracture of the upper portion of the left tibia.

The wound was débrided within a few hours and was treated with sulfathiazole powder, vaseline gauze and a circular cast from the toes to the upper thigh.

The dressing was not removed until he reached this hospital January 8, 1945, at which time there was evidence of moderate suppuration with fragmentation of the tibia.

Operation of sequestrectomy and ostectomy was performed January 10, at which time several long splinters of necrosed bone were removed. Culture of the wound revealed Bacillus proteus, which on

testing was inhibited by 250 units of penicillin per cubic centimeter. A large defect in the tibia and soft tissues 10 centimeters in length, 2.5 centimeters in width, and 3 centimeters in depth was allowed to fill in with blood clot. Several drops of penicillin in normal saline solution, 1000 units per cubic centimeter, were injected into the blood clot on the first and third postoperative days. The surface of the clot was overlaid with a thin coating of penicillin jelly. The clot organized with moderate retraction, and was covered with split-thickness skin grafts on February 7. All grafts were successful, and healing of the wound was complete on March 1, 1945.

EXTENSIVE LOSS OF SOFT TISSUE WITH EXPOSURE OF BONE

Exposed bone is a deterrent to wound healing because of its tendency to degeneration and necrosis as long as it remains uncovered, even though infection is held in check. Therefore an effort is made to cover the exposed bone with soft tissue at the earliest favorable time. Good results have been obtained by placing split-thickness skin grafts directly on bone after gross evidence of necrosis and infection has disappeared, even though wound cultures remain positive. The skin-grafted surface is treated with compression dressings moistened every other day with normal saline solution containing 1000 units of penicillin per cubic centimeter, and compression is maintained for a period of 8 to 10 days. This procedure was used in 5 cases in which an infected open wound had been present for from 6 to 28 months. All except 1 healed completely. The single case of failure was a tibial compound fracture wound which had remained open with bone exposed for 20 months following metal plating. There was no gross evidence of bone necrosis or suppurative infection following operation of skin grafting, and it is probable that failure was due to inadequate circulation in the exposed bone.

CASE 20. Skin grafting of exposed bone surface following treatment with penicillin jelly (Fig. 2).

Patient, aged 21 years, was injured by shrapnel in overseas combat April 9, 1943, receiving a perforating wound of the distal third of the femur with loss of the patella.

Treatment prior to his arrival at this hospital April 8, 1944, consisted chiefly of blood transfusions and plasma infusions, penicillin intramuscularly, closed cast treatment, and two operations of sequestrectomy.

Examination here disclosed a large open wound on the anterior of the lower third of the thigh with an irregular perforating wound of the femur. The wound was treated with sulfathiazole ointment dressings until October 17, at which time the bone was saucerized to encourage overgrowth of soft tissue.

Topical penicillin in normal saline solution every 4 hours was started November 6, 1944. Cultures at this time showed the presence of nonhemolytic Staphylococcus albus and Bacillus proteus. The profuse suppuration was lessened, but ingrowth of soft tissue over the large area of exposed femoral bone was negligible.

Penicillin jelly treatment was started December 15, 1944, and the suppuration subsided completely within 10 days. Split-thickness skin grafts were applied over an area of exposed bone 5 centimeters in length and 2 centimeters in width on January 11, 1945. All of the grafts remained viable and the wound was completely healed on January 25, 1945.

Secondary wound closure by suturing was usually not possible because of the loss of bone substance and the loss of overlying soft tissues. Only 2 cases in the series were suitable for this procedure. One of these, described in the following case history, illustrates the favorable effect of the procedure on a fractured femur which had shown little tendency to unite before the wound was closed secondarily.

CASE 21. Secondary wound closure by suturing (Fig. 3).

Patient, aged 24 years, received a bullet wound November 24, 1943, which caused a fracture of the middle third of the left femur. He was treated in traction, followed by hip spica cast until May 30, 1944.

He refractured the femur June 17, 1944, while out of cast, and was admitted to this hospital 1 month later. Examination here disclosed a comminuted simple fracture of the middle third. The extremity was put in traction. An abscess formed in the soft tissues in the region of the fracture and this was drained August 22, 1944. His condition, which had been critical, improved rapidly following adequate drainage. However, drainage continued unabated. A large femoral fragment showed evidence of advanced degeneration, and showed little tendency to unite to the proximal and distal main fragments. The soft tissue wound was intractable to treatment with sulfathiazole ointment, and showed little response to instillations of azochloramide solution and penicillin solution used successively.

Penicillin jelly treatment was started December 12, 1944, and was continued until January 12, 1945. At that time the trough-shaped wound, measuring 15 centimeters in length and 2 centimeters in depth, showed no suppuration, and was epithelialized ex-

cept in its depth. Secondary closure of the wound was performed January 12, 1945. The wound remains completely healed after a period of 4 months, and the femur shows evidence of increase in callus formation with apparent union.

INACCESSIBLE WOUNDS WITH SINUS TRACTS

There have been several cases of deep sinus tracts in which it was inadvisable to explore the depth of the wound by surgical operation. These patients were examined roentgenologically following injection of a radiopaque medium into the tracts through a soft rubber catheter after making certain that there was free exit for any substance injected. Following this examination to determine the extent of the pockets of infection, penicillin jelly was injected into the sinus tracts every other day. The merit of the use of penicillin jelly in these cases lies in the fact that it is apparently harmless when it is retained in the wound. One of the patients treated in this manner, a pelvic abscess secondary to a bullet wound through the sacrum, is of especial interest.

CASE 28. Healing of inaccessible wound with sinus tract (Fig. 4).

Patient, aged 24 years, received an accidental .45 caliber bullet wound on June 12, 1943, the bullet entering the left gluteal region, piercing the middle third of the sacrum, tearing segments of small bowel and sigmoid, and lodging in the pelvis. The intestine was repaired 2 hours later.

A large subpubic abscess was drained June 25, 1943, and a left retroperitoneal abscess was drained August 12, 1943.

A flexion deformity developed gradually in the left hip, and the hip became ankylosed with destructive changes in the joint cartilage. The earlier drainage of the pelvic abscesses had resulted in a persistent sinus emerging in the left lower anterior abdominal wall. In November, 1943, x-ray of the tract, with iodized oil as a contrast medium, showed ramifications extending toward the crest of the left ilium, the hip joint, and the ischium.

A total of 20,300,000 units of penicillin was given intramuscularly from February to August, 1944. Cultures of hemolytic streptococcus from the tract were reported during this period.

Exploratory surgical incision was made in the left hip region over the greater trochanter on March 22, 1944. There was no pus found in the hip joint. An abscess broke through the exploratory hip incision on April 5, 1944. A subsequent pelvic operation performed July 26, 1944, was unsuccessful in arresting the drainage from the sinus in the left hip region.

The patient was transferred to this hospital September 10, 1944. At that time all surface wounds were closed except the sinus tract emerging at the left hip. Wound culture showed nonhemolytic Staphylococcus albus, nonhemolytic streptococcus, and Bacillus proteus. The bullet was removed from the pelvis November 30, 1944. There was no change in the drainage of pus from the sinus tract of the hip following this surgical procedure. No pus was seen in the vicinity of the bullet at the time of its removal.

X-ray examination following injection of the sinus tract with radiopaque medium showed essentially the same findings as those previously described, with the exception that the abscess in the lower left pelvis was more clearly defined.

Injections of penicillin jelly into the sinus tract were started January 16, 1945. The injections were made every other day through a No. 12 soft rubber catheter, 2 cubic centimeters of the jelly being instilled with very moderate pressure. The tract became completely closed on January 30, 1945, for the first time since the development of the sinus on March 22, 1944, and has now remained closed for a period of 6 months. The white blood cell count and temperature remain normal and the patient is completely well except for an almost complete ankylosis of the left hip joint.

It is possible that removal of the bullet played a part in the healing in this case; but the fact that no communication was demonstrated between the bullet and the abscess at the time of operation, and the fact that the purulent drainage, which had continued for 6 weeks following operation, ceased promptly after penicillin jelly instillations would argue for penicillin jelly being the major factor.

INFLUENCE OF GENERAL DISTURBANCES ON WOUND HEALING

General factors which should be given consideration are the state of body nutrition, the character and volume of blood, protein sufficiency, vitamin balance, and concurrent diseases. It is difficult or impossible to measure the degree of departure from normal with ordinary methods in most of these factors except when the departure from normal is extreme. Nevertheless, it must be accepted that such disturbances do exist in chronic suppurative infections and that they should be considered as factors in influencing healing.

Protein insufficiency is a constant accompaniment of prolonged, severe suppuration, and a high protein diet is important in helping to overcome this deficiency. This is especially important for the soldier returned from a distant outpost where some essential foods are

lacking, and certain types of malnutrition are prevalent. Edema of the tissues in and around the wounds is interpreted as serious protein deficiency if circulatory cause can be ruled out. It has not been considered necessary to measure the proteins of the blood or to determine the albumin-globulin relationship except in patients with pronounced edema.

Vitamins which are known to be of importance in wound healing, particularly vitamin C, have been found to be low in most of the cases in this series. The need for this vitamin and vitamin B complex in greater quantities in those suffering from suppurative disease, or in those who are undergoing wound healing, has been satisfactorily demonstrated by research workers. The diet is supplemented with liberal amounts of orange juice, and in addition to this a supplement of vitamin C is given intramuscularly if the patient shows a low vitamin C blood level. These include patients showing less than 0.8 milligram per 100 cubic centimeters of blood.

A continued low blood level that does not improve with transfusions and adequate diet is usually due to suppuration. In such cases attempt is made to control infection by removal of sequestra or improvement of drainage.

Optimum circulation in the injured part is maintained by proper elevation, by application of warmth in cases of vascular injury, and by bandaging and splinting in such a manner as to prevent unequal pressure with its consequent accumulation of venous blood in the region of the injury. In this connection the principles of supportive and compressive bandaging used in the treatment of varicose ulcers applies equally well to established compound fracture wounds of the leg.

Local and general physical conditioning of the patient is continued throughout the treatment, except during periods immediately following major operations of sequestrectomy, drainage, or wound revision. Exercises are directed toward the conditioning of muscles in the affected extremity and muscles in general. This phase of therapy is especially important in patients whose wounds require months for healing

SUMMARY

1. A method of topical application of penicillin in lubricating jelly in the treatment of established infection in compound fracture wounds is described. It has the advantage of maintaining high concentrations of penicillin in the area of the wound without the use of cumbersome technique or apparatus.

2. Evidence is presented of the effectiveness of this preparation in permeating the barriers in the zone of infection. This is in contrast to parenteral administration in which relatively small amounts of penicillin reach the area of suppuration.

3. Twenty-eight compound fracture wounds with established infection have been treated by this method. They had been refractory or slow in response to accepted methods of therapy for periods varying from 2 to 27 months, and all except 2 have shown a highly satisfactory response to treatment with penicillin jelly.

4. Delay in the healing of old infected compound fracture wounds is most frequently due to the presence of necrosed bone. The presence of devitalized bone sets up a vicious circle in the wound by encouraging infection which in turn causes further necrosis of bone. Penicillin jelly has proved itself to be effective in breaking up the vicious circle by eliminating or minimizing infection even in the presence of necrosed bone, and by inhibiting the soft tissue and bone infection after the sequestra are removed.

5. Skin grafting, secondary wound closure and healing by organization of blood clot have been successful in most instances in the patients in this series treated with penicillin jelly. From the author's experience and the experience of others, such procedures would seem to have been less successful without its use.

6. Topical penicillin therapy is to be considered as a part of a general plan of treatment. Good surgical judgment, proper surgical technique, maintenance of an optimum circulation in the injured part, and maintenance of a proper state of nutrition are absolute essentials in the treatment.

IS THE BIOPSY OF NEOPLASMS DANGEROUS?

An Experimental Study

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CLINICIANS are prone to avoid the incision or removal of neoplasms for fear that the diagnostic procedures may serve to disseminate tumor cells, but the reluctance to obtain a biopsy specimen for histologic study often delays adequate therapy and invalidates an accurate diagnosis. It is generally accepted as a truth—and there is some experimental evidence to support the belief—that the rupture of the capsule of a tumor or the destruction of adjacent tissue structures incurred in obtaining a biopsy specimen may serve to open vascular and lymphatic channels to tumor cells. Physicians, therefore, avoid manipulation of suspected tumors in order to prevent local extension or metastases. These concepts imply that the extent of neoplasms can be roughly judged by gross inspection and that tumor metastases are usually limited by the observed tissue barriers.

Clinical evidence supports the theory that any degree of trauma either accidental or surgically intended may serve to disseminate a malignant tumor and, in rare instances, to alter the nature of a benign growth. Thus students are cautioned by their elders not to squeeze or unnecessarily disturb a tumor; indeed, at times only a single student of an eager class is favored with an opportunity to touch gingerly the "restrained new growth." Thus medical novitiates learn to regard any new lump fearfully as though its mysterious walls might disintegrate if the tumor cells were disturbed. This acquired fear of tumor dissemination is readily increased as the physician may unjustly attribute rapid and abundant embolic phenomena to his operative intervention in a seemingly localized new growth.

If one should accept the aforementioned theses that a tumor growth is completely localized by its capsule, by adjacent tissue barriers, or by unyielding vascular channels, then interruption of such defenses might lead to a sudden catastrophe with rapid invasion of local and distant parts. However, a critical study of surgical and postmortem specimens gives ample evidence that neoplasms are not restrained or unduly inhibited by their capsules or areas of marked desmoplasia since metastases may precede capsule formation and emboli may readily flow in lymphatic channels found in encircling tissue barriers. There is also adequate evidence to suggest that tumor emboli may occur throughout the life of a tumor and that growth in distal parts depends on the adaptability of the invaded tissues to the repeated attacks of viable emboli. It would not be unreasonable, therefore, to think that inoculation of an organ with a large mass of tumor cells might well produce a viable metastatic focus while an embolus of only a few cells might succumb to tissue defenses. Hence, a decrease in the bulk of a neoplasm available for metastases should serve to decrease the incidence of metastatic tumor growth. The most likely danger, therefore, from cutting into a tumor would be the mechanical transfer of neoplastic cells to the operative incision. This accident seldom follows careful operative procedures.

If one examines the medical literature relative to the danger of biopsy procedures, it is obvious that the experimental evidence is contradictory and inconclusive. It is, therefore, not surprising that clinicians are in a quandary when confronted by a suspected malignancy. The value and the dangers of biopsy were stressed in the medical literature in 1917 (3), when it was proposed to submit biopsy specimens to the Health Department of New York City. In the heat of the controversy editorials and numerous articles written by clinicians vigorously condemned the practice of obtaining such specimens. Well known surgeons of

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that day referred to a biopsy as a criminal act, since "incision into a breast tumor renders the prognosis grave or hopeless." The late Dr. Ewing, however, was of the opinion that a clean surgical incision produced no untoward results and pointed out that the diagnosis was often impossible without histologic study. Tyzzer, in 1913, demonstrated that daily massage increased the number of metastases in experimentally produced tumors in animals. F. C. Wood, in 1919, injected rats with small pieces of a carcinoma and after several weeks excised parts of the tumor in one group and the entire tumor in a second group. Animals of a third group were used as controls. The animals were sacrificed in 3 to 4 weeks. The percentage of metastases in the third group, that in which biopsy specimens were not obtained, was 32 while in the first group the percentage of metastases was 22. In the group in which the tumors were completely excised the percentage was 21.8. In 1922, Knox, in the same laboratory, inoculated mice with a transplantable tumor and massaged the resulting growths daily. These inoculated animals and the animals of a control group were sacrificed 4 weeks following inoculation. It was apparent from this experiment that massage promoted metastases. Marsh, working with spontaneous tumors in mice, found that massaging these breast tumors increased the percentage of pulmonary metastases.

In a carefully controlled clinical study Peterson and Nuttall selected two groups of squamous cell carcinomas of which the size, treatment, and course could be readily observed. From one group a biopsy specimen was removed with no attempt to control the degree of trauma. In the control group diagnosis was made upon clinical inspection. Both groups of tumors were treated in a similar manner and followed for a period of 2 years. At the end of this period the 166 cases in the two groups were reviewed, and it was found that the incidence of metastases had not been increased by the biopsy procedure.

After reviewing the available experimental evidence, Peyton was of the belief that the harmful effects of trauma had not been completely proved. He had the clinical impression that infiltration of a tumor with local anesthesia could disseminate a neoplasm. He injected mice with various tumors. In one group the tumors were subsequently removed under general anesthesia while in another group local anesthesia was applied about the tumor. In the latter group, in which metastases were usually infrequent, pulmonary nodules were abundant following the injection of the local anesthesia. He concluded that the use of local anesthesia for the removal of a neoplasm might be a dangerous procedure.

Since present medical opinion and experimental evidence are not entirely in accord it seemed desirable to investigate the problem further employing more biologically uniform material. With the development of relatively homogenous inbred stocks of rats and mice and a diversity of carcinogenic agents, the experimenter has at his command a limitless array of transplantable tumors with 100 per cent predictability of progressive growth. By the transplantation of small fragments from an induced or spontaneous tumor into any organ or tissue of other hosts of like genetic constitution the experimenter may duplicate many thousands of times, if desired, the growth of the same neoplasm. The difference between these transplanted tumors and the same tumor in the primary host is that the causative agent is not operative in the secondary hosts. However, such material is ideally adapted to the study of the effects of any procedure on tumor growth.

MATERIAL AND METHODS

The transplanted tumors used in the present experiment arose spontaneously or were induced in relatively homogenous inbred rats and were transplanted into hosts of the same inbred line. All were progressively growing neoplasms which had been propagated by transplantation from 6 to 150 generations previously.

For the first experiment IRS 4337, a very malignant Cysticercus-induced fibrosarcoma was selected. The history on transplantation of this tumor has been previously described by Dunning, Curtis, and Bullock (1). The rats were inoculated on the right forefoot with 2 milligram grafts of a tumor from the 150th transplanted generation. Nine days after in-

TABLE I.—THE AVERAGE SURVIVAL PERIOD AND TUMOR WEIGHT AND PERCENTAGE OF METASTASES OBSERVED IN OPERATED UPON AND UNOPERATED UPON RATS BEARING TRANSPLANTED TUMORS

Exper. No.	No. of rats	Type of tumor	Group	Days survived	Tumor wt. removed (gm.)	Metastasis					
						Lymph node		Lungs		Skeleton	
						No.	Per cent	No.	Per cent	No.	Per cent
1	19	Fibrosarcoma	Control	28	21	15	79	17	90	0	
	19		Biopsy	42	34	12	63	16	84	0	
2	19	Adenocarcinoma	Control	98	24	1	5	5	26	0	
	20	breast	Biopsy	125	15	3	15	12	60	0	
3	20	Adenocarcinoma	Control	110	61	0		3	20	0	
	18	breast	Biopsy	113	39	0		4	22	0	
4	34	Squamous	Control	93	15*	33	97	31	91	25	74
	20	cell carcinoma	Biopsy	95	13*	20	100	18	90	15	75

*Average weight of superficial metastases.

oculation when the tumors averaged about 0.5 centimeter in diameter they were completely excised. No attempt was made to remove a margin of healthy uninvolved tissue. The skin was secured with one or two interruptured sutures.

The tumor used in the second experiment was R 2426, a spontaneous papillary cystadenocarcinoma of the mammary gland. A study of the growth of this tumor on transplantation has been reported by Eisen. Fragments weighing approximately 3 milligrams of a tumor from the 31st generation were inserted under the skin of the right side by means of a trochar. This tumor grows relatively slowly and the biopsy was not performed until 60 days after inoculation when the tumors weighed approximately 5 grams. An incision about 1 centimeter in length was made with a knife through the skin and a wedge shaped slice of tissue about 0.2 centimeter at the margin was removed. Since the tumors were somewhat cystic and hemorrhagic a considerable amount of bloody fluid and tissue exuded through the incision when the capsule was cut. When the hemorrhage subsided the wound was cleansed and closed with a suture.

Rats bearing transplanted adenocarcinoma of the 10th generation of R2572 were used for the third experiment. The primary tumor was a mixed tumor of the mammary gland. The separation of the epithelial portion has recently been described by the authors (2). The tumors were implanted similarly to R2426 and 22 days after transplantation when they weighed approximately 5 grams a simple biopsy was performed. This tumor is fairly firm in consistence and only a small mass of tissue was removed and the wound closed with a suture.

For the fourth experiment rats bearing transplanted squamous cell carcinoma $\frac{\text{M-C } 951}{7\text{ A}}$ were used. The primary tumor was induced by a 3 milligram pellet of methylcholanthrene in the prostate gland of an agouti Irish male rat of the 24th BxS generation of AxC line 9935 and has not been previously reported. Transplanted tumors of the 7th generation were used for this experiment and the biopsies were performed 20 days after implantation when the tumors weighed approximately 5 grams as in the two previous experiments.

Following the biopsy the tumors were allowed to grow until death of the rat occurred. A careful postmortem examination of the biopsied and control series included measurement and weight of the neoplasm and examination of the superficial lymph nodes, lungs, and skeleton for metastases. The lungs were injected with 10 per cent formalin and preserved with a section of the tumor and the lymph nodes for microscopic examination.

All preserved tissues were examined thoroughly. The biopsied series were compared with the control series for the average number of days which they survived after transplantation and for the percentage with metastases.

RESULTS

The results are summarized in Table I. In the first experiment 19 rats of the control series bearing fibrosarcomas survived an average of 28 days after inoculation. The tumor removed postmortem weighed an average of 21 grams; 15, or 79 per cent, of the rats had lymph node metastases and 17, or 90 per cent, were found to have lung metastases. In the experimental series the 19 rats which had their tumors excised 9 days after inoculation survived an average of 42 days. The difference in average survival period of 14 ± 3.8 days is statistically significant and represents the equivalent of nearly a year and a half in a man's life. The average weight of the tumors was 34 grams and larger than the tumors of the control series but the percentage of lung and lymph node metastases was not increased, being respectively 84 and 63 per cent.

In the second experiment 19 rats of the control series bearing adenocarcinoma $\frac{\text{R } 2426}{32 \text{ A}}$ survived an average of 98 days. The tumors weighed an average of 24 grams and only 5, or 26 per cent, had lung metastases. One, or 5 per cent, had axillary lymph node metastases. The 20 rats in the experimental series survived an average of 125 days. The average tumor weight was 15 grams. Three, or 15 per cent, had axillary lymph node metastases and 12, or 60 per cent, had lung metastases. The difference in average survival period of 27 ± 8.5 days in favor of the rats operated upon is also statistically significant and represents the equivalent of nearly 3 years in a man's life. The tumors were smaller than in the control series, averaging only 15 grams. The difference in average weight of the tumors in this series was probably due to more extensive ulceration and the prolongation of average survival time was a result of the removal of a considerable mass of the tumor in the operative procedure. The significant increase in percentage of lung metastases was a result of the increased survival period. Figure 1 shows the length of survival of each rat in the two series, with the individuals which showed microscopic and gross lung metastases designated by cross-hatched and blackened bars respectively. In the control series 3 rats in which lung metastases were discovered by microscopic examination survived 80, 96, and 100 days. Three rats in which no lung involvement was detected survived 101, 108, and 117 days, and the 2 rats with extensive gross metastases survived for 164 and 165 days. Among the rats operated upon microscopic lung metastases were observed in 3 rats, which survived respectively, 89, 89, and 95 days. Three rats died after 106, 110, and 247 days, respectively, with no lung involvement, and all but 2 which died after 106 and 117 days, respectively, of those with gross lung metastases survived any of the control series which died without lung involvement.

In the third experiment 20 rats of the control series bearing $\frac{\text{R } 2572}{10 \text{ A}}$ survived an average of 110 days after transplantation. The tumors weighed an average of 61 grams and only 3, or 20 per cent, had lung involvement. In the experimental series 18 rats with biopsied tumors survived an average of 113 days with tumors which averaged 39 grams and 4, or 22 per cent, had lung involvement. There were 2 additional rats in this series in which the tumors practically ulcerated out following the operation. These two hosts survived for 276 and 373 days, respectively. Both had large tumors at necropsy. One had lung and lymph node involvement and the record on the other was lost. In this experiment employing a tumor of firm consistence in which the biopsy specimen comprised only a small fraction of the mass of the growth, no prolongation of survival period was noted and no difference in the percentage of metastases was detected, except in the 2 instances noted in which secondary infection following the operation inhibited the growth of the tumor.

In the fourth experiment 34 rats of the control series bearing $\frac{\text{M-C } 951}{7 \text{ A}}$ survived an

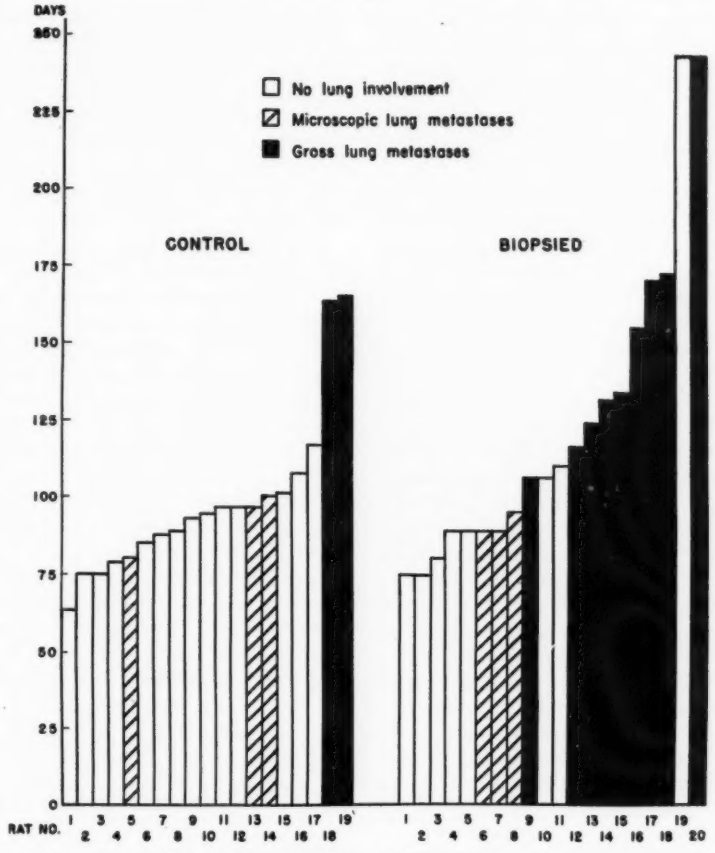

Fig. 1. The survival period and incidence of lung metastases of operated upon and unoperated upon rats bearing transplanted adenocarcinoma $\frac{R\ 2426}{32\ A}$.

average of 93 days and the 20 rats of the experimental series in which the tumors were biopsied 20 days after inoculation survived an average of 95 days. Since these tumors characteristically ulcerate early the tumor weight in both series was based on the combined weight of the superficial lymph node metastases. In the control series the lymph node metastases averaged 15 grams compared with 13 grams in the experimental series. In the control series 31, or 91 per cent, had lung metastases while 18, or 90 per cent, of the experimental series had lung involvement. Skeletal metastases were observed in 74 per cent of the control series and in 75 per cent of the experimental series. In this experiment like the preceding one in which the biopsy specimen was not a factor in the mass of the growth no difference was detected in survival time or percentage in which lymph node, lung, or skeletal metastases were observed.

COMMENTS

The concept held by many clinicians that a biopsy may enhance the growth of a neoplasm has long needed further investigation. It is generally recognized that it is often impossible by inspection alone to distinguish benign from

malignant tumors; hence it is usually necessary to obtain a biopsy specimen. If physicians were to avoid incising suspicious lesions to obtain a biopsy, then the early diagnosis of cancer would obviously be impossible. Unfortunately it is difficult to evaluate the effect of trauma on malignant tumors of man since the heterogeneous hereditary patterns of the hosts differ and the observed tumors seldom are identical in either their gross or their microscopic features.

In the observations recorded here in which homogeneous strains of inbred rats were inoculated with equal portions of the same transplanted tumors, one could ascertain the effect of surgical trauma on the neoplasms. It is noteworthy from examination of Table I that if one removes a portion of a tumor, he increases the length of life of the animal; this increased survival is due presumably to the decrease in the quantity of cells available for growth. Such data confirm the recent clinical observations (10) that the surgical removal of all available tumor tissue in a seemingly hopeless case serves to prolong the individual's life for several years. Further, no untoward effects are recorded by cutting into the tumor mass or by severing lymphatic channels. A survey of these reports and a study of the data reported here would suggest that the treatment of a neoplasm is facilitated by the removal or destruction of any quantity of the growth and that the hosts' survival is, thereby, proportionately prolonged.

SUMMARY

1. Rats bearing transplanted fibrosarcoma, adenocarcinoma, and squamous cell cancer were operated upon and compared with an unoperated upon control series for length of survival after transplantation and percentage in which metastases were detected.

2. The average survival period of rats bearing transplanted fibrosarcomas was significantly prolonged by excision of the tumor 9 days after transplantation but the percentage of lung and lymph node metastases was not altered.

3. The average survival period of rats bearing transplanted adenocarcinoma was significantly prolonged by the removal of a considerable mass of the tumor 60 days after inoculation. The rats operated upon which survived the rats of the control series had a significantly higher percentage of lung metastases.

4. A simple biopsy performed on rats bearing transplanted adenocarcinoma did not affect the average survival period of the rats or increase the percentage with lymph node and lung metastases.

5. A simple biopsy of transplanted squamous cell cancer did not affect the average survival period of the rats or increase the percentage of metastasis to the lymph nodes, lungs, and skeletons.

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CHRONIC OSTEOMYELITIS COMPLICATING WAR COMPOUND FRACTURES

An Evaluation of 125 Patients Treated by Early Secondary Closure

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THE remarkable success observed following delayed primary closure of war wounds on or after the fourth day following initial débridement and of late secondary closure following excision, either by direct suture or closure with skin flaps or grafts (Churchill), stimulated our efforts toward early closure of wounds in the treatment of chronic osteomyelitis complicating war compound fractures. We adopted a plan of conservative ostectomy followed by wound closure on the fifth postoperative day, in cases in which such closure was mechanically possible and appeared warranted; and penicillin was used both systemically and locally.

Observations, herein recorded and initiated September 15, 1944, have been directed toward answering the following questions:

1. What is the value of penicillin, systemically and locally, in war osteomyelitis?
2. What is the optimum time for ostectomy?
3. What shall be the extent of the ostectomy?
4. What is the value of early secondary wound closure not only in diminishing the immediate convalescent period with a minimum amount of scarring and deformity, but in preparing the field more adequately and more quickly for definitive reconstructive work, when such surgery will be necessary?

On our service we have accepted a minimum waiting period, *following cessation of all drainage*, of 3 months prior to definitive soft tissue reconstructive surgery and of 6 months prior to reconstructive bone surgery, and we are convinced, following our own experience and that of others, that shorter periods invite an increased incidence of recurrent infection. Despite our anxiety to reduce this time factor, we do not accept the method of widespread extirpation of soft tissue and bone recently advocated in the treatment of war osteomyelitis, as the drive to eliminate infection surgically appears greatly to exaggerate the already existing soft tissue and osseous reconstructive problems (Kelley, Rosati, and Murray).

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TECHNIQUE

Soft tissue is not sacrificed indiscriminately. The sinus tract and necrotic skin margins are excised and *the ostectomy is limited to the removal of bone that is obviously dead and detached*. Any bone that appears viable is spared. Sharp edges and prominences are not removed except when they might interfere with wound closure.

The skin is undermined freely. In some cases this procedure has been carried to fully one-half of the circumference of the extremity. However, there has been no spread of infection by such extensive dissection. It often permits complete skin closure or at least a considerable diminution in the size of the wound gap. Mattress sutures of silkworm gut or wire are used in conjunction with buttons to prevent cutting-in of the skin. The upper and lower portions of the wound are closed and the central portion is left open, one or two sutures being placed in readiness for closure on the fifth postoperative day.

A vaseline gauze or rubber drain is inserted into the depths of the central portion of the wound and plaster of Paris fixation is applied. Usually the posterior one-half of the previous cast is utilized and completed with a few circular bandages. On the fifth postoperative day the drain is removed through a fenestrum and the sutures are closed *if the appearance of*

TABLE I.—SERIES A. ANALYSIS OF 75 PATIENTS TREATED WITH SYSTEMIC AND LOCAL PENICILLIN

Completely healed wounds			
Postoperative drainage Duration	No. patients	Involvement Bone	No.
10 days	6	Tibia	33
30 days	14	Tibia, fibula	3
6 weeks	7	Fibula	2
2 months	14	Femur	16
3 months	12	Metatarsal	5
4 months	6	Ilium	4
5 months	5	Os calcis	5
6 months	2	Astragalus	1
7 months	4	Cuboid	1
8 months	1*	Radius	1
9 months	1†	Humerus	1
10 months	1‡	Metacarpal	1
Total	73		
Persistent drainage			
7.5 months	1	Neck of femur and hip joint; reoperation 8-27-45	
8 months	1	Upper tibia and knee; probable reoperation	
Total	2**		

*Lower femur and knee joint
†Lower tibia and ankle joint
‡Os calcis, reoperation and healing 10 days later
**Both ceased draining 2 to 3 months after reoperation

the wound warrants it. These sutures are removed on the tenth postoperative day and the cast is closed for 1 month. Subsequent external fixation will depend on the appearance of the wound and the progress of bony union.

Femur cases are returned to balanced suspension with skeletal or skin traction, depending on the state of bony union.

In cases in which complete skin closure has not been possible or advisable, healing of the residual skin defect has been materially hastened by the early application to receptive surfaces of either split skin grafts or large pinch grafts.

There have been some cases, with extensive loss of soft tissue, in which this method of delayed skin approximation has not been applicable. Here the extensive surfaces have been covered, even in the presence of considerable drainage, with intermediate skin or pinch grafts. In some of these cases, in which the defect has existed over bony prominences or easily traumatized areas or in the preparation of the field for definitive reconstructive measures, more adequate skin coverage has been found necessary following this temporary "skin dressing."

Dose of penicillin. Systemic. Penicillin has been employed intramuscularly in 15,000 to 30,000 unit doses every 3 hours, beginning at 6:00 p.m. on the evening prior to surgery, and has been continued postoperatively for a minimum of 10 days. Total dosage has varied from 1,200,000 units, in mild and moderately severe cases, to 2,400,000 units in the severe cases of osteomyelitis. More recently a uniform dosage of 40,000 units every 4 hours has been adopted (Keefer, *et al.*). Our patients have invariably preferred periodic intramuscular injections to continuous administration by vein or muscle. The antibacterial agent was discontinued in 6 patients because of severe skin reactions, without mishap, and there were 3 instances in which a clinical picture of nonspecific reaction was manifest toward or shortly following the completion of the course of penicillin—reactions attributed to impurities in the commercial preparations.

Local. Penicillin instilled in 20 cubic centimeter doses 3 times daily (250 units per c.c. of sterile water) was employed in the first group of 75 cases, a $\frac{3}{16}$ inch rubber tube having been introduced through a stab incision into the depths of the wound. This treatment was eliminated in the second group of 50 cases for purposes of comparison.

EVALUATION OF CLINICAL MATERIAL

Series A consists of 75 cases of chronic osteomyelitis treated by ostectomy and delayed closure and the use of penicillin, both systemically and locally, between September 15, 1944, and March 1, 1945, and evaluated up to September 15, 1945 (Table I).

Of this group, in 73 patients (97.2%) the wounds are completely healed, while in only 2 cases (2.8%) are they still draining. It will be observed that in 41 cases (54.7%) healing was complete within 2 months and that wound healing occurred in another 31 cases following drainage periods *up to 9 months*, a total of 72 healed without reoperation. One patient with involvement of the os calcis was reoperated upon following a 10 month postoperative drainage period. Several well localized sequestra were removed, the cavity walls col-

TABLE II.—SERIES B. ANALYSIS OF 50 PATIENTS TREATED WITH SYSTEMIC BUT NO LOCAL PENICILLIN

Completely healed wounds

Postoperative drainage Duration	No. patients	Involvement Bone	No.
10 days	12	Tibia	14
30 days	21	Femur	6
6 weeks	7	Femur (great trochanter)	2
2 months	5	Humerus	6
4.5 months	1	Ileum	4
		Radius and ulna	2
		Radius	2
		Ulna	1
		Fibula	2
		Os calcis	2
		Metatarsal	2
		Tarsus	2
		Scapula	1
Total	46		

Persistent drainage

4 months	1	Tibia, knee joint	
3 months	1	Os calcis	
2 months	1	Femur	
6 weeks	1	Tibia, knee joint	
Total	4		

lapsed, and the wound healed 10 days later. Of the 2 patients with persistent drainage following initial ostectomy, one, with a localized osteomyelitis of the femoral neck, has been reoperated upon 7.5 months later, while the other, with extensive infection in upper end of tibia and knee joint draining 8 months after operation, may require a second ostectomy.[1]

Cases of osteomyelitis at the ends of long bones with adjacent joint involvement have proved to be very recalcitrant. In one patient with chronic infection at the distal end of femur and involvement of the knee joint healing occurred after 8 months of postoperative drainage, in another, with involvement of distal end of tibia and ankle joint, healing was complete 9 months postoperatively.

Series B consists of 50 patients treated in like manner, but without local penicillin. Ten patients were operated on between September 15, 1944, and October 15, 1944, and the remaining 40 between April 14, 1945, and July 6, 1945; all have been evaluated up to September 15, 1945 (Table II). In this series B, wounds are completely healed in 46 (92%) patients, and in only 4 (8%) are they still draining. It

[1]Both cases ceased draining 2 to 3 months following reoperation. In other words, healing has occurred in all 78 cases, or 100 per cent.

TABLE III.—ANALYSIS OF 73 PATIENTS WITH HEALED SOFT TISSUE WOUNDS (SERIES A)

Time required for wound healing after ostectomy	No. patients	Average period of preoperative drainage months	Union	Large defect	Non-union
10 days	6	6.5 (4 to 11)	6		
11 to 30 days	14	5.0 (2 to 7)	14	2	
6 weeks	7	4.7 (2 to 7)	7		
2 months	14	3.8 (2 to 10)	8		6
3 months	12	4.0 (1.5 to 6)	8	1	4
4 months	6	4.2 (3 to 6)	4	3	2
5 months	5	4.0 (3 to 5)	4	2	1
6 months	2	3.0	2	1	
7 months	4	4.1 (3 to 5)	4	2	
8 months	1	4.0	1	1	
9 months	1	4.0	1	1	
10 months	1	3.0	1	1	

will be noted that in 45 cases (90%) healing was complete within 2 months after operation.

No significant information has been obtained in an evaluation of the theaters of operations from which our patients have been derived. This observation also applies to the bacterial growths obtained from the wounds, which revealed several types of penicillin-sensitive staphylococci and/or streptococci, with a variety of other organisms which were often insensitive to penicillin. The latter groups did not appear to inhibit wound healing materially, although contributing to the amount and odor of drainage, and they tended to disappear as healing progressed.

EVALUATION OF STUDY

1. Value of penicillin. A comparison of the progress of wound healing in those patients treated early in Series A, in whom penicillin was first employed very cautiously and in total doses from 250,000 to 750,000 units, with those treated later with more adequate total doses (1,200,000 to 2,400,000 units) has convinced us that penicillin, systemically administered, is of definite benefit in the treatment of this type of chronic osteomyelitis. Although our operative technique has not varied in these cases, there are other variable factors present which make the evaluation of penicillin a purely relative one and not accurately measurable, viz., the duration of pre-

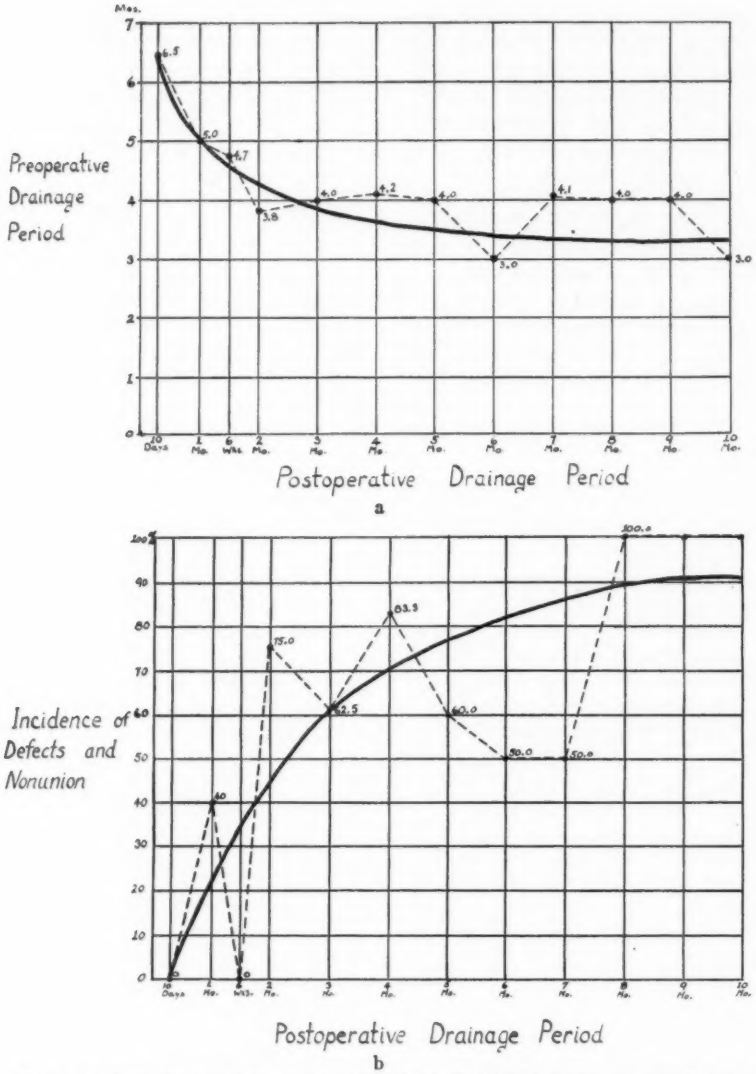

Fig. 1. Analysis of 73 cases of chronic osteomyelitis with healed soft tissue wounds (series A). a, Relation between preoperative and postoperative drainage periods. b, Relation between postoperative drainage period and large bone defects and/or nonunion.

operative delay, the severity and extent of the fracture and of the complicating infection, and the anatomic site of the infectious process.

It is believed from a comparison of Series A and B that the *local* use of this agent has not served materially to alter the progress of wound healing, and for this reason its local use has been discontinued. Thus the nursing problem required by repeated local instillations is eliminated.

2. Optimum time for ostectomy. The value of adequate preoperative delay. Our patients have

often required whole blood for secondary anemia and a diet high in protein and vitamin C. Extensive drainage has been materially lessened during this waiting period by a preliminary course of penicillin. Elevation of the affected extremity has diminished edema, and simple exposure of the wound has served to improve the condition of the soft tissues which are often macerated and inflamed from prolonged exposure to drainage. Adequate preoperative delay, which has been tolerated well in all instances, not only encourages improvement in the patient's general condition but insures more accurate delimitation of the infection and permits progress of bony union.

A study of the figures in Table III and of the graphs in Chart 1 demonstrates a striking relationship between the duration of the preoperative and the postoperative drainage periods and the incidence of large bone defects and/or disturbances of bony union.

In an analysis of the 73 healed cases in Series A, most rapid postoperative wound healing (10 days) occurred in those with the longest preoperative delay (average, 6.5 months). This must, therefore, be interpreted as the optimum waiting period in this series. It will be observed that *as the period of delay prior to ostectomy has lessened, the period of postoperative drainage has lengthened, and the incidence of bone defects and of nonunion has mounted.* In other words, adequate preoperative delay encourages a shortening of the postoperative drainage period, which means lessened soft tissue scarring. It also ensures more accurate delimitation of the bone infection, which in turn permits easier definition and less sacrifice of bone by the surgeon at the time of ostectomy, less residual bone defects and a greater likelihood for firmer bony union.

It may be argued that, for example, a preoperative waiting period of 2 months with postoperative drainage for 4 months represents no greater loss than a 4 month waiting period with only 2 months of postoperative drainage. This is far from true, for the case with the shorter postoperative period of drainage will show healing of soft tissues with less scarring, will probably have had less bone sacrifice at the time of sequestrectomy, and bony union will be more secure.

3. Extent of ostectomy. Conservative bone excision. Only bone that is obviously dead and detached is sacrificed. Prominences and irregularities are not removed except when they may interfere with wound closure. Protruding bone is excised to the level of the surrounding granulation tissue. Bone thus spared may aid materially in diminishing the problems of bone defects and of delayed union. The wisdom of this attitude is exemplified in an early group of patients in Series A in whom all apparently infected bone was resected boldly, with resultant bony gaps, shortening, and deformity, and with prolonged drainage notwithstanding, and who have been faced with extensive programs of reconstructive surgery. We dislike the term "saucerization" in the surgery of these cases, for the creation of a saucer-like topography of necessity implies the sacrifice of adjacent normal bone and the exaggeration of pre-existing defects.

We have observed that extreme conservatism must be exercised particularly in the excision of bone in certain regions, as for example in the lower end of the femur, the upper end of the tibia, and in the os calcis. Indiscriminate resection, because of the lack of adequate bone reformation in these particular areas, serves to create considerable reconstructive problems, prolongs convalescence, and delays functional restoration. We have observed a number of these cases, given sufficient time, fill in spontaneously with scar, while the residual column of bone has been sufficiently sturdy to assume adequate functional responsibility. Thus far only 2 patients with upper tibial defects will require plastic reconstructive measures of any magnitude. Collapse of the walls and elimination of the cavity appear worthwhile in selected instances of chronic osteomyelitis of the os calcis.

A few areas, of which the ilium and fibula are examples, lend themselves very well to a liberal extirpation of involved bone, since this sacrifice leads to no disability whatever, yet often ensures successful delayed closure.

4. Value of delayed wound closure. The extensive undermining of skin, performed to permit a complete or partial closure following ostectomy, has not resulted in the spread of infection in any instance. This procedure

offers a rapid method of closure with adequate skin, lessens the need for skin plastic measures, ensures less scarring and a more satisfactory bed for reconstructive surgery of underlying muscle, tendon, nerve, and bone.

CONCLUSIONS

1. Penicillin, administered systemically in adequate doses, is of value in the treatment of chronic osteomyelitis complicating war compound fractures. Its local use has not assisted materially in wound healing and has been discontinued.

2. The purpose of early skin closure following ostectomy in the treatment of war osteomyelitis is to encourage healing of these wounds with the least amount of scarring and deformity. This result is obtained most ideally when the skin flaps may be coaptated directly, as herein described.

3. Adequate preoperative delay ensures a more accurate delimitation of the infectious process. This serves to lessen the amount of bone that need be sacrificed at the time of ostectomy and allows for progression of union at the fracture site, for if this is secured, the treatment of the osteomyelitis becomes considerably simplified.

4. These factors—the healing of soft tissues with the least scarring and deformity, the sacrifice of the least amount of bone and the occurrence of union at the fracture site—all serve to lessen some of the more complicated problems in the reconstructive surgery of extremity war wounds.

It is our firm belief, and our statistics bear this out, that the conservative approach herein described, assures greater likelihood for the satisfactory control of war osteomyelitis *with the least sacrifice of soft tissue and bone.* Other methods in use elsewhere, where the drive to eliminate infection carries with it the widespread extirpation of soft tissue and bone, serve to exaggerate and complicate the reconstructive problems already present in these cases.

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PERSISTENCE OF THE VITELLINE (OMPHALOMESENTERIC) ARTERY AS A CLINICAL PROBLEM

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DEVELOPMENTAL anomalies originating in the embryonic vitelline, or omphalomesenteric, structures are predominantly those associated with Meckel's diverticulum. Much less common than persistent elements of the vitelline ductal system are anomalies arising from the vitelline vascular system. Despite their rarity, persistent omphalomesenteric vascular remains were recognized and described in the latter part of the eighteenth century. That they may be of singular importance as a clinical problem is attested by the ensuing discussion.

EMBRYOLOGY

Review of the embryologic development and, consequently, of persistent anomalies of the vitelline (omphalomesenteric) circulation begins with consideration of the yolk sac. In the human embryo the yolk sac, sometimes called the umbilical vesicle, is demonstrable in the earliest known specimens, i.e., at the end of the second week (11). Its nutritive function is probably of minor significance but its entodermal lining gives rise to the mucosal epithelium of the major part of the digestive tract while the mesodermal layer of its wall is the site of early development of blood cells and vascular channels (1, 3). Primitive "blood islands" of the vascular anlage have been demonstrated in the mesodermal layer of the yolk sac wall of the Peters and von Spee embryos (13½ to 18 days of age, 12). As the yolk sac enlarges and as the primitive gut develops, the two structures become connected to one another by the so called yolk stalk, or vitelline (omphalomesenteric) duct, which elongates as the embryonic body increases in size. Subsequently, the yolk sac atrophies and the vitelline duct becomes incorporated into the umbilical cord. It detaches itself from the gut during the sixth week of intrauterine life. Normally, the duct degenerates after its detachment. However, persistence of its intra-abdominal portion occurs in 2 to 3 per cent of cases, manifesting itself definitively as the familiar Meckel's diverticulum of the ileum.

Like the vitelline duct, existence of the vitelline circulation is transient. At the fifth week of intrauterine life, the omphalomesenteric artery is the most prominent ventral branch of the aorta. It arises from the latter by several roots and, passing ventrally toward the umbilical cord, divides to surround the primitive gut by an arterial ring at the point of junction of the gut with the omphalomesenteric duct (Fig. 1). In its subsequent course, it is paired so that two vitelline arteries are identifiable in the early embryo (5 weeks). The paired vessels leave the embryo accompanied by the vitelline duct and are distributed as a ramifying plexus over the surface of the yolk sac. Coincidentally with atrophy and degeneration of the yolk sac, one of the paired vitelline arteries disappears. The remaining one develops further and comes to lie in the mesentery of the midgut, supplying the latter with blood and becoming definitively the superior mesenteric artery (Fig. 2). According to Cullen, its connection with the umbilical cord may persist long after the vitelline duct has disappeared, which normally occurs at approximately the sixth week of intrauterine life. Whatever may be the temporal relationship, the vitelline artery normally loses its umbilical attachments to remain as the superior mesenteric artery.

The vitelline veins, arising in the wall of the yolk sac, are paired. The two vessels enter the abdominal cavity of the embryo at the umbilicus accompanied by the vitelline artery and duct. From the umbilicus the two venous trunks course cephalad, following the path of the gut, to empty into the primitive heart. At the fifth week of embryonic development, the liver bud begins to expand and interrupts the vitelline veins in their course toward the heart. One of the vessels becomes incorporated for the most part in the growing hepatic sinusoidal system while the other atrophies and disappears. The surviving vessel receives the superior mesenteric vein and the splenic vein just before entering the liver and becomes finally the portal vein.

CLINICAL SIGNIFICANCE

Persistence of the omphalomesenteric artery manifests itself anatomically as an adventitious, intra-abdominal cord covered by peritoneum. Usually it is attached firmly at its two extremities,

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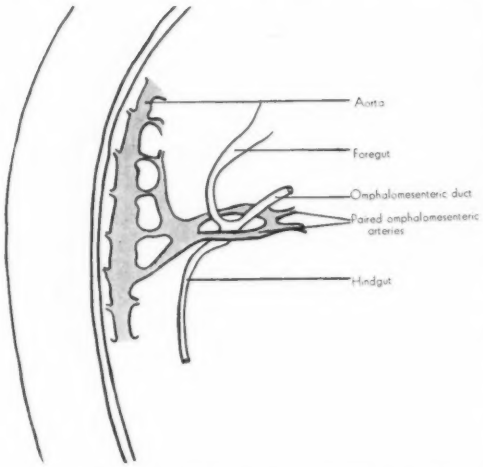

Fig. 1. Origin of paired omphalomesenteric arteries from primitive aorta in the early embryo (5 weeks). Note relationship to junction of the omphalomesenteric duct and intestine.

one to the anterior abdominal wall at the umbilicus and the other to the mesentery of the terminal ileum. By such an arrangement, there is formed a tense band traversing the abdominal cavity in an anteroposterior direction. Its potential danger as a source of intestinal obstruction is obvious. Persistent vitelline arterial remnants may be associated with a Meckel's diverticulum, in which instance a free band is formed connecting the diverticular mesentery to the umbilicus or to the ileal mesentery; the resulting anatomic arrangement is a ring or loop through which coils of intestine may pass to become strangulated. The least common form of persistent vitelline artery is that situation in which the vascular remnant is attached only at its mesenteric end, the remainder of the vessel hanging free in the abdominal cavity.

Clinically, it is significant that only 4 cases of persistent omphalomesenteric artery producing no symptoms have been reported. Of these, only one was an adult, a dissecting room cadaver studied by Derbes and Hoge, showing both persistent artery and Meckel's diverticulum; the case record contained no mention of abdominal discomfort during life. The others were infants examined at autopsy, in 2 of whom the anomalous vessels were unattached at one end, hanging harmlessly free in the abdomen (Meckel and Ruge), while the third was a newborn child found to have both mesenteric and umbilical attachments intact (Gesil). Inasmuch as 3 of the asymptomatic patients were infants, it is striking that the literature provides only one adult patient showing no clinical disturbance as a result of persistence of the vitelline artery.

Table I contains a summary of the literature of 12 cases of persistent vitelline artery in which disturbing clinical symptoms were present. Nine of the cases terminated fatally, a mortality rate of 75 per cent. All but one of the deaths were due to acute intestinal obstruction. The remaining fa-

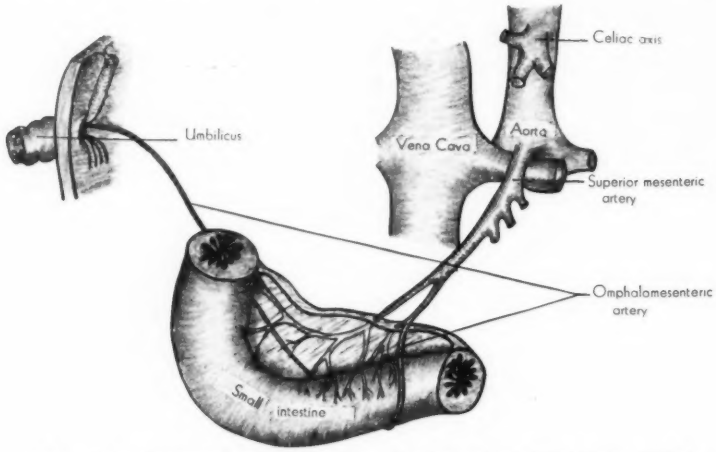

Fig. 2. Semidiagrammatic representation of relationship of persistent omphalomesenteric artery to superior mesenteric artery at term. Normally, the omphalomesenteric vessel loses its umbilical attachment before term.

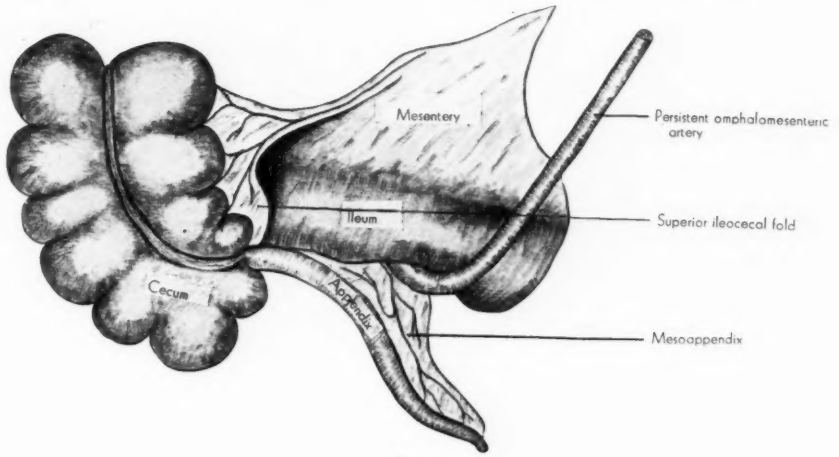

Fig. 3.

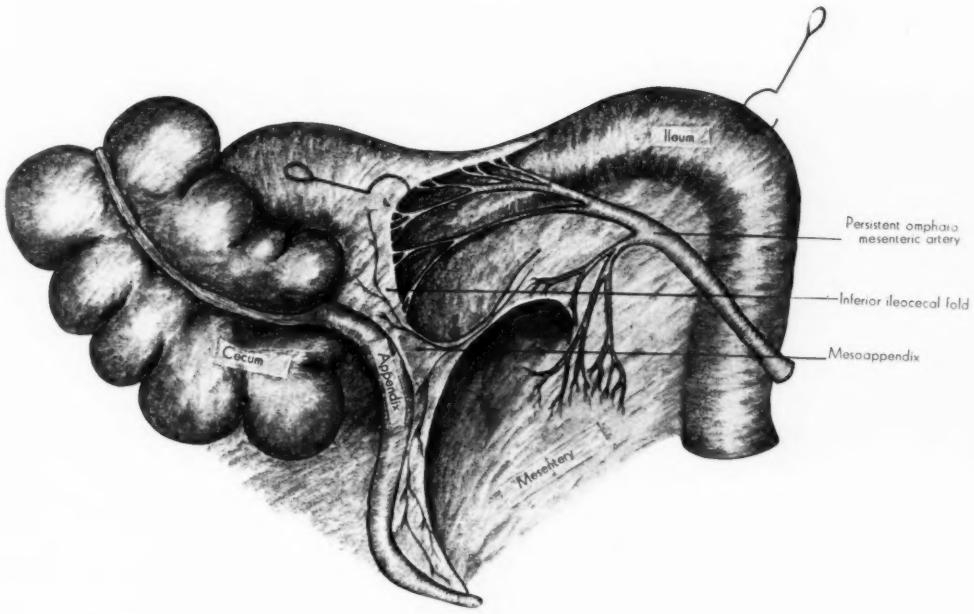

Fig. 4.

Fig. 3. The relationship of persistent omphalomesenteric artery to ileum and cecum as seen at the time of operation.

Fig. 4. Ileum retracted upward showing terminal branches of persistent omphalomesenteric artery entering mesentery.

tality occurred in a child 4 months of age as a result of hemorrhage from a branch of the persisting vitelline artery. This patient, recorded by Fraser and McCartney, presented a small area of granulation tissue in the umbilicus. Actual cauterization of the granulating surface was

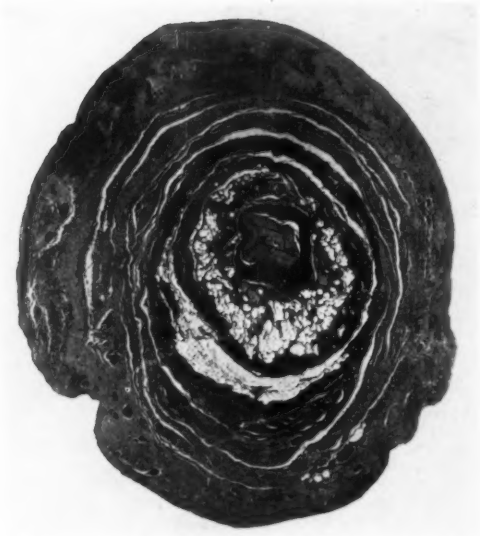

Fig. 5. Cross section of excised cord showing central artery surrounded by fibroelastic and areolar tissue with external serosal coat. (Weigert elastic tissue stain, × 21.)

Fig. 6. Central artery of excised cord showing well defined internal and external elastic laminae. Note patent lumen containing red blood cells. (Weigert elastic tissue stain, × 114.)

undertaken, necessitating traction upon a pedicle to which the cauterized tissue was attached. Death occurred 48 hours later. Autopsy examination revealed the pedicle to be the vestigial omphalomesenteric artery and the tension placed upon it by traction had caused rupture of a small branch near its mesenteric attachment with subsequent fatal hemorrhage into the abdominal cavity.

Of the 8 patients dying of acute mechanical ileus, Meckel's diverticulum was present in 6. In each instance, the persistent vitelline remnant connected the diverticular mesentery to either the umbilicus or the ileal mesentery, thus forming a loop or ring through which segments of intestine had passed to become strangulated. The remaining 2 fatal cases of ileus showed persistence of the omphalomesenteric artery alone, no diverticulum being found. Mahomed's patient was an 18 year old boy in whom the persistent artery extended from the anterior abdominal wall to the mesentery of the terminal ileum where it joined branches of the superior mesenteric artery. The tense vascular cord had looped about the ileum with resultant complete obstruction of the bowel. Postoloff's case, the most recent to be reported, was a 38 year old man who was first seen 4 days after the onset of his illness and who presented typical clinical evidence of acute obstruction of the small intestine. A history of numerous previous attacks of abdominal pain was elicited. The patient died shortly after admission to the hospital and postmortem examination revealed the presence of a persistent vitelline artery. The vessel was demonstrable as a "firm, round, tapering cord covered by peritoneum" and extended from the umbilicus to the mesentery of the terminal ileum 20 centimeters proximal to the ileocecal junction. The small intestine was found to have looped itself about the band and was completely obstructed.

Three cases have been reported in each of which the surgical removal of a persistent vitelline artery accomplished complete disappearance of disabling symptoms. None was diagnosed before operation. Shaw recorded the case of a 43 year old woman who had complained of right lower abdominal pain since childhood. During the course of a hysterectomy for vaginal bleeding, the patient was found to have a persistent artery extending from the anterior abdominal wall to the ileal mesentery and transfixing the omentum to hold it immobilized under tension in the right lower abdominal quadrant. Excision of the vascular

TABLE I.—COLLECTED CASES OF PERSISTENT VITELLINE ARTERY CAUSING CLINICAL SYMPTOMS

Author	Date	Age of patient	Pathologic findings
Sandifort	1793	Adult*	Sacciform diverticulum attached by tough cord, "resembling in structure the round ligament of the liver," to cecal mesentery and forming a noose to constrict the intestine causing fatal obstruction.‡
Eschricht	1834	"Old woman"*	Meckel's diverticulum attached by persistent vitelline artery to ileal mesentery forming a loop which caused fatal strangulation of intestine.
Falk	1835	20 yrs.	Persistent vitelline artery uniting free end of Meckel's diverticulum with ileal mesentery forming a congenital loop. Strangulation of intestine.
King	1843	14 mos.	Patent Meckel's diverticulum, adherent to umbilicus, forming enteric fistula. Persistent vitelline artery connecting diverticulum to ileal mesentery producing "band" compression of small intestine with fatal obstruction.
Mahomed	1875	18 yrs.	Persistent vitelline artery extending from umbilical region to mesentery of terminal ileum, looping about latter causing complete intestinal obstruction, fatal. No diverticulum.
Fitz (Case 1)	1884	28 yrs.	Persistent vitelline artery attached at free end of Meckel's diverticulum and at mesentery of ileum forming congenital ring through which small intestine had passed. Fatal strangulation of bowel.
Fitz (Case 2)	1884	21 yrs.	Meckel's diverticulum adherent at distal end to umbilicus (patent?). Persistent vitelline artery, passing from mesentery of diverticulum to umbilical region, forming loop through which small bowel had herniated to cause fatal strangulation.
Fraser and McCartney	1920	4 mos.	Granulation tissue attached to a pedicle in umbilicus. Actual cauterization performed, necessitating traction on pedicle which caused rupture of small branch of persistent vitelline artery near mesenteric junction, producing fatal intra-abdominal hemorrhage. No diverticulum.
Shaw	1925	43 yrs.	Persistent vitelline artery extending from anterior abdominal wall to ileal mesentery transfixing omentum and holding it immobilized in right lower abdominal quadrant. Pain since childhood. Cured by excision of arterial band. No diverticulum.
Gautier	1931	21 yrs.	Previous history of repeated attacks of right lower abdominal pain. At operation for suspected appendicitis, persistent vitelline artery found extending from umbilicus to ileal mesentery 15 cm. from cecal junction. Cured by excision of arterial band. No diverticulum.
Buchanan and Wapshaw	1940	12 yrs.	History of intermittent colicky abdominal pain in right lower quadrant and periumbilical region accompanied by vomiting. Laparotomy revealed persistent vitelline artery extending from umbilicus to ileal mesentery 30 cm. from cecum. No obstruction of bowel at time of operation. No diverticulum.
Postoloff	1946	38 yrs.	History of repeated episodes of cramping abdominal pain for two years. Last attack fatal. Autopsy showed persistent vitelline artery extending from umbilicus to mesentery of terminal ileum 20 cm. from cecum, causing "band" obstruction of small intestine. No diverticulum.

*—Not given in original report.
‡—Described in Fitz's (7) comprehensive review as "probably the first on record."

remnant resulted in prompt disappearance of the long-standing abdominal discomfort. Gautier's patient was a 21 year old man who complained of repeated attacks of right lower abdominal pain with remissions and exacerbations. Celiotomy revealed the presence of a persistent omphalomesenteric artery attached at the umbilicus and extending to the ileal mesentery 15 centimeters from the ileocecal junction. Following surgical removal of the adventitious band, the patient remained asymptomatic. The most recent report, by Buchanan and Wapshaw, of an operative cure was that of a 12 year old boy who had "suffered from intermittent attacks of colicky abdominal pain, coming on at intervals of about 3 weeks." His illness had endured for 3 months with progressive increase in severity. At laparotomy, a cord was found "substantially anchored" to the umbilicus at one of its extremities and to the mesentery of the ileum at its other, 30 centimeters from the ileocecal junction. Histologic examination confirmed the presence of arterial elements in the cord. It was the authors' impression that intermittent intestinal obstruction had been produced by the vascular anomaly. The patient's recovery was uneventful after excision of the band, and he was completely relieved of his preoperative symptoms.

Persistence of the omphalomesenteric veins is extremely rare, only 2 cases having been reported. Spangenberg, in 1819, reported the occurrence of a persistent vitelline vein, discovered at autopsy, in the body of a 20 year old man; it was productive of no symptoms. Buchanan and Wapshaw occupy the unique position of having recorded an instance of persistent vitelline vein as well as the case of arterial remains here noted. The former patient was a man 20 years of age. History and physical

examination were confirmatory of a diagnosis of acute intestinal obstruction. Exploration of the abdomen revealed a stout cord attached at the umbilicus and passing posteriorly to disappear in the retroperitoneal tissues just below the third portion of the duodenum. In its course, the cord had encircled a segment of intestine causing complete obstruction of the closed-loop type. The patient died on the fifth postoperative day. Histologic studies confirmed the presence of venous elements in the adventitious band.

CASE REPORT

Roper Hospital No. 39778. A Negro laborer 35 years of age was admitted to the hospital June 29, 1945, complaining of abdominal pain of 6 months' duration. He stated that his pain was intermittent in character, located in and around the umbilicus and in the epigastric midline between the xiphoid and the navel. The pain was exaggerated by standing, walking, straining, coughing, and remaining erect for long periods of time. It was said to be completely relieved by reclining. For this reason, the discomfort was noticed rarely at night. Near the end of a day's work, the patient revealed that the pain was at its worst and that vomiting occasionally occurred under such circumstances. There was no radiation of the pain and it was not influenced by eating or hunger. There was no history of hematemesis, bloody or tarry stools, jaundice, constipation, or diarrhea. History of the other body systems was noncontributory.

Physical examination revealed the following: temperature, 98.6°; blood pressure, 140/75; pulse and respiration normal. The patient was a well developed and well nourished Negro in no acute distress but obviously in pain. Abdomen was flat and moved with respiration. There was no distention, muscle spasm or rigidity, and no masses were palpable. Tenderness was present on pressure upon the umbilicus but was not excessive; rebound pain was absent. On auscultation, peristalsis was audible and of normal character. Rectal examination was negative. Remainder of examination showed only irrelevant findings.

Laboratory studies showed white blood cell count 9,300 with normal differentia' count; hemoglobin, 12 grams. Urinalysis showed normal urine. Analysis of gastric contents showed normal findings. X-ray of gastrointestinal tract after ingestion of barium showed no abnormalities. Blood Wassermann and Kline tests were negative.

A specific diagnosis was not made but in view of the persistent nature of the patient's discomfort and because he was incapacitated by his illness, laparotomy was done 3 days after admission.

Under spinal anesthesia, the patient's abdomen was entered through a right paramedian incision. A firm, extremely taut fibrous cord, covered by peritoneum, was found attached at one extremity to the under surface of the umbilicus and at the other to the mesentery of the terminal ileum 3 centimeters from the ileocecal junction (Fig. 3). The band did not enter the lumen of the ileum. Dissection at the mesenteric attachment revealed the terminal portion of the cord to fan out into numerous small, fibrous, filamentous strands which lost themselves between the two leaves of the mesentery (Fig. 4). The main cord looped over the ileum to the left of the latter in such a way as to support in part the weight of the terminal ileum and cecum when the patient was erect (Fig. 3). However, there was found to be no agglutination of the ileal serosa to the covering of the adventitious band so that there was no evidence of obstruction or compression of the intestine. Furthermore, the cord was not adherent to any other viscera along its course to the umbilicus. Traction upon the anomalous structure at its ileocecal extremity caused dimpling and inversion of the umbilicus as observed from without. Further exploration revealed no abnormalities of the abdominal viscera. There was no Meckel's diverticulum. The cord was clamped and ligated at its two extremities and excised in its entirety. After removal of the appendix, the abdomen was closed in layers.

Follow-up examinations at 4 and 10 weeks after operation have found the patient to be entirely free of pain. He has returned to work and is considered to be cured.

Pathologic examination of the removed specimen, which measured 9 centimeters in length, revealed a tough cord covered by peritoneum. Microscopic study of the sections, selected from various segments of the cord, demonstrated a centrally located, thick walled, patent artery surrounded by a zone of loose fibrofatty tissue, a layer of more compact subserosal areolar tissue, and an external covering of serosa (Fig. 5). Higher magnification of the central artery showed a well defined internal elastic lamina and a patent lumen containing red blood cells, some of them in rouleaux formation (Fig. 6).

The occurrence of abdominal pain in this patient was apparently on a mechanical basis. Review of Figures 3 and 4 explains the traction type of discomfort which was noticed only when the individual was standing erect. In this position, the gravity effect was such that the full weight of the cecum and, most probably, several loops of small intestine, in addition to the terminal ileum, was exerted upon the adventitious band. This in turn produced traction upon the peritoneal surface of the umbilicus. In the recumbent position, tension of the cord was reduced materially and the umbilical traction eliminated. Vomiting, which was said to occur at the peak of intensity of the pain, was more likely of the reflex origin, due to traction upon the periumbilical parietal peritoneum, than to actual obstruction of the bowel.

Of interest is the fact that no symptoms referable to the abdomen occurred until the patient was 35 years old. While difficult to explain, it is significant that the patients reported by Mahomed and by Buchanan and Wapshaw developed their first symptoms after 18 and 12 years respectively. Postoloff's case was 36 years old before noticing abdominal discomfort. On the contrary, Shaw's patient, who was 43 years of age, had suffered from lower abdominal pain since childhood.

Intestinal obstruction is the most common (and most serious) complication of persistent omphalomesenteric vessels. That no evidence of ileus was found either at operation or in the patient's history may be regarded as coincidental. In respect to the production of symptoms by vitelline vascular remains in the absence of mechanical obstruction, the case is similar to those reported by Shaw and by Gautier. It is probable that intestinal obstruction would have supervened

eventually if the adventitious band had not been removed.

SUMMARY

1. The embryologic development of the vitelline vascular system is reviewed briefly.

2. A review of the literature of persistent vitelline vascular elements is presented in tabulated form and their clinical significance discussed.

3. A case of persistent vitelline artery causing disabling symptoms which were relieved by operation is reported.

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A STUDY OF THE EFFECT OF PROPHYLACTIC ORAL SULFADIAZINE UPON INFECTION IN SOFT TISSUE WAR WOUNDS CLOSED SECONDARILY

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THE well controlled statistical studies of Meleney and his associates has cast serious doubt upon the efficacy of systemic sulfonamides in preventing infection in traumatic wounds. This present study, on the other hand, although dealing with a somewhat different problem, indicates that sulfadiazine, given orally at secondary closure of soft tissue war wounds, reduces the incidence of infection and is associated with better healing.

The multiplicity of factors involved in wound healing makes the critical evaluation of any one factor difficult. It is difficult to carry out controlled and impartial experiments in a laboratory; the problems are greatly increased when one deals with patients rather than guinea pigs; and under war conditions it may at times appear impossible to obtain sufficiently accurate and detailed records, or observe the patient long enough to assess results. Furthermore, in the treatment of battle casualties the emphasis is upon producing the best immediate results by any and all means; a relatively inocuous drug like sulfadiazine is likely to be freely used if it promises any conceivable benefit to the patient, rather than withheld in selected cases to help determine its true value.

In the treatment of the 200 soft tissue wounds which form the basis for this study, it must be admitted at the outset that the aim was to procure the best possible results in each case, and not to conduct an experiment on the prophylactic value of sulfadiazine. The situation has been further complicated by the fact that in some instances penicillin as well as sulfadiazine has been employed prophylactically. (Penicillin was not available for routine use in the light injuries which constituted most of the wounds.) Nevertheless, the very fact that wounds which promised difficulty were treated with prophylactic sulfadiazine, lends weight to any differences which can be shown to favor the sulfadiazine treated group, since it may be assumed that the bulk of the worst wounds will be included there.

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It is perhaps worth mentioning at this point that little was expected from sulfadiazine as a prophylactic when the series was begun; in common with many other surgeons we regarded it with a skeptical eye. It was first used in those patients who had wounds which promised trouble (as in deep wounds, or wounds which closed with considerable tension) or in whom good healing was of particular importance (as in wounds with associated damage of a peripheral nerve). Stock was taken after 150 wounds had been closed, and the value of the drug appeared sufficiently established to warrant its routine use.

It might seem from the difficulties detailed in the foregoing paragraphs that no valid conclusions could possibly be drawn in this report. Some advantage may derive from the fact, however, that the series is both consecutive and in every sense a personal one. The writer supervised the preparation of the wounds for closure, employed a uniform technique in operating upon them, and personally observed their postoperative course. This at least eliminated the inevitable differences in judgment between individuals as to when a wound is ready to close, how it should be closed, and what constitutes a wound complication.

MATERIAL AND METHODS

Material. The series consists of 200 consecutive, personally performed secondary closures upon soft tissue wounds in 131 soldiers; 40 of the wounds were in 29 German prisoners of war; 151 wounds were caused by high explosive fragments; 47 wounds were caused by bullets, and 2 by nonbattle trauma. The wounds were all incurred in France and Germany between August, 1944, and April, 1945. In all but 7 wounds, preliminary débridement was carried out in forward hospitals and the patients transported to this general hospital anywhere from 1 to 25 days after the débridement. Compound fractures were excluded from the series, as were wounds in certain patients being promptly evacuated for other conditions (such as cerebral injury) which precluded a satisfactory period of observation. During this entire time it was the fixed policy of the surgical service

to close either by suture or graft all wounds at the earliest practicable time. Recognized exceptions were: wounds so small that they could be expected to heal spontaneously within 2 weeks; deep wounds with small openings; wounds presenting severe and persistent infection (not more than 2 or 3 wounds were excluded for this last reason during the entire period). In general, closure was preferred to grafting whenever it could be effected.

Ninety-three wounds represent a consecutive series for the entire hospital; that is, every secondary closure performed in the hospital was carried out by the writer during this time, to prevent an artificial selection of easy cases for the series. (Actually, all wounds which promised difficulty in closure have been consistently turned over to the writer because of his interest in the problem.) The final results in the entire series are comparable to other published series of secondary closures. Seventy-eight per cent of the wounds were solidly healed in 2 weeks or less.

Preparation of the wound. The appropriate time for closure was determined by the gross appearance of the wound. No closure was performed at the first dressing, but wounds which were clean when first seen were closed after a day or two of saline or azochloramide dressings. Wounds which were dirty or infected were treated with meticulous dressings of 1:3000 aqueous solution of azochloramide once or twice daily, at which time slough was picked off piecemeal. (In 3 or 4 cases a secondary débridement was necessary, followed by secondary closure a few days later.) Edema or induration at the wound edges was permitted to subside. Once the wound was grossly clean, secondary closure was carried out. In some wounds appreciable delay in closure and even in the start of systematic preparation took place because of the press of more urgent work.

Operative procedure. The procedure carried out depended entirely upon the physical character of the wound, and fell roughly into one of three general types. In those wounds supple enough to permit it (chiefly those received within 10 days of débridement) a *simple closure* was performed with widely spaced, deeply placed vertical mattress sutures of silk, usually a heavy silk; sutures were not buried. Heavily scarred wounds were *excised en bloc,* and closure carried out with buried sutures of fine silk or cotton and vertical mattress sutures of the same material to the skin. There was an intermediate group in which there might be undermining of skin edges, or excision of exuberant granulation tissue, or modification of the shape of the wound to facilitate closure; these have been grouped as *wound revision.* In this group buried sutures of fine silk or cotton might or might not be used. Catgut was not used in any wound. In an occasional wound with marked tension, retention sutures over gauze pledgets were employed. In some of the wounds treated early in the series, sulfanilamide powder was lightly dusted into the wound; this was discontinued later. There were no instances of so-called "partial" closure in this series.

TABLE I.—WOUND COMPLICATIONS

Wounds having more than one complication have been listed here only once under the most serious. Any infection has been given priority over any technical complication.

	Number	Total
Uncomplicated healing		90
Infection		
Mild stitch abscess	11	
Moderate cellulitis	5	
Stitch abscess	23	
Severe cellulitis	3	57
Wound abscess	6	
Infection with lymphatic spread	4	
Late infection (after apparent healing)	5	
Non-infectious or technical complication		
Separation at suture line	27	
Sinus from drain	6	
Cutting sutures	7	
Mild induration	8	53
Hematoma	2	
Dehiscence from tension	2	
Dehiscence from unobliterated dead space	1	
		200

Chemotherapy. The usual scheme for the employment of sulfadiazine as a prophylactic was to begin it as soon after the secondary closure as the patient could take it; 4 grams was given as an initial dose, and this was followed in an hour by a 1 gram dose, after which he received 1 gram every 4 hours for 6 days. The penicillin dosage was 20,000 to 30,000 units intramuscularly every 3 hours for 2 to 5 days. Nine patients with 19 wounds were given sulfadiazine before as well as after closure; 2 patients with 3 wounds received penicillin as well as sulfadiazine before and after. These are not treated as a separate group since any advantage possibly resulting from the preclosure use of sulfadiazine is still a feature of its prophylactic value. There were only 2 instances of untoward reaction to sulfadiazine—both febrile—among the 92 patients who received the drug.

Postoperative care. In general, patients who had wounds of the lower extremity were kept in bed until healing was sound. Splints were freely employed. Sutures were removed from the sixth to tenth day depending upon the appearance and

TABLE II.—INCIDENCE OF INFECTION AND DELAYED HEALING (15 DAYS OR MORE) IN WOUNDS GROUPED BY FACTORS ACTING PRIOR TO SECONDARY CLOSURE

Factor	Total wounds	Infection			Delayed healing		
		Number	Per cent	Significant difference	Number	Per cent	Significant difference
All wounds	200	57	29	—	44	22	—
All wounds excluding 3 technical failures	197	57	29	—	41	21	—
Cause of wound							
Bullet	47	13	28		9	19	
High explosive	148	44	30	No	32	22	No
Other	2	—	—		—	—	
Type of wound							
Perforating wound	47	23	49	Yes	15	32	No
All others	150	34	23		26	17	
Size of wound							
Large*	101	35	35	No	23	23	No
Small	96	22	23		18	19	
Nationality							
German prisoner	38	23	61	Yes	13	34	Yes
U.S. soldier	159	34	21		28	18	
Time of débridement from injury							
24 hrs. or less	141	42	30	No	29	21	No
25 hrs. or more	56	15	27		12	21	
Chemotherapy at time of injury							
None or questionable	36	18	50	Yes	13	36	No
Sulfadiazine ± Penicillin	85	25	29		18	21	
Delay—débridement to closure							
10 days or less	91	17	19	Yes	14	15	No
11 days or more	106	40	38		27	25	
Preparation of wound at general hospital							
7 days or less	140	31	22	Yes	26	19	No
8 days or more	57	26	46		15	26	

*Large wounds: those 6 cm. or more in length, or 3 cm. or more in width.

location of the wound; emphasis was placed upon supporting the suture line with adhesive strapping (which was often applied immediately after operation as well). Sulfadiazine was employed therapeutically in 7 instances, and penicillin in 4 instances after infection had appeared in a wound. Their use in these cases has not been regarded as prophylactic, although they may have contributed to the swifter healing of the wound. In 1 case particularly penicillin appeared to abort a serious cellulitis.

Appraisal of complications. This feature of the study is of paramount importance. Ideally, a single person, other than the surgeon, should follow all the wounds, since surgeons are sometimes reluctant to see blemishes in their own handiwork. Unfortunately this ideal arrangement could not be followed, but the writer made an honest effort to be both strict and uniform in applying criteria of wound healing, and to note even the most minor complications. Some evidence of strict interpretations is to be found in the fact that although 78 per cent of the wounds were healed in 2 weeks or less, 55 per cent are listed as having a complication of one sort or another (Table I).

Complications were recognized as of two general types: technical and infectious. A hazy line may separate a "cutting suture" from a "mild stitch abscess," or "induration" (as seen in a wound closed under tension) from "moderate cellulitis," although average examples in each group usually are clear enough. Wounds having both infection and a technical complication have been listed only once under the heading of infection. In each group of cases the wound was listed only under the most severe complication which it presented.

TABLE III.—INCIDENCE OF INFECTION AND DELAYED HEALING (15 DAYS OR MORE) IN WOUNDS GROUPED BY FACTORS ACTING AT TIME OF SECONDARY CLOSURE OR LATER

Factor	Total wounds	Infection			Delayed healing		
		Number	Per cent	Significant difference	Number	Per cent	Significant difference
All wounds excluding 3 technical failures	197	57	29	—	41	21	—
Anesthetic							
Local	51	17	33	No	13	26	No
General*	146	40	27		28	19	
Number of wounds closed at operation							
Single wound	92	26	28	No	16	17	No
Two or more	105	31	30		25	24	
Aerobic culture of wound at operation							
No pathogenic strains	12	0	0	Yes	1	9	Yes
One or more pathogenic strains	63	33	52		19	30	
All cultured wounds	75	33	44	—	20	27	—
Operative procedure							
Wound excision	92	34	37	Yes	18	20	No
Simple closure	66	11	17		14	21	
Wound revision	39	12	31	No	9	23	No
Topical sulfanilamide							
Used	53	21	40	No	11	21	No
Not used	144	36	25		30	21	
Wound tension at closure							
Moderate or marked	26	7	27	No	7	27	No
Not significant	171	50	29		34	20	
Drainage of wound							
Wound drained	17	4	24	No	5	29	No
Wound not drained	180	53	29		36	20	
Chemotherapy at time of closure							
No chemotherapy	44	21	48	Yes	16	36	Yes
Oral sulfadiazine	107	23	21		12	11	
Oral sulfadiazine ± Penicillin	143	34	24		23	16	
Penicillin only	10	2	20	—	2	20	—

*General anesthesia includes two spinal anesthesias.

The total healing time from secondary closure was determined for each wound. Here again there is latitude in interpretation, but a wound was not regarded as healed until epithelization was complete. In all but 2 or 3 instances the patient was kept under observation a sufficient length of time to determine the primary fate of the wound. In these exceptions the patients were transferred out 7 to 10 days after secondary closure, but healing seemed to be progressing normally at that time. In 5 cases it was possible to record the onset of a late complication a week or more after apparent sound healing of the wound. It is necessary to point out, however, that in many cases the development of a late complication would not have come to our attention, since the patient was promptly discharged to duty when thought fit, and readmission would have been more than likely at another hospital. This is an important but unavoidable limitation of the study.

ANALYSIS OF DATA

The following facts stimulated the present study: 44 wounds received no chemotherapy at the time of closure; infection developed in 21 or 48 per cent; 107 wounds received oral sulfadiazine at the time of closure; infection developed in 23 or 22 per cent. The difference is statistically significant(1). Rather than being a final conclusion, this fact can only be the starting point of a detailed investigation, since in a series this small, it might well be a result of an artificial selection of wounds, or the unsuspected operation of other factors. For example, the 107 wounds in which sulfadiazine was employed might have been the smallest, soonest treated and cleanest wounds of

TABLE IV.—COMPARISON OF INCIDENCE OF INFECTION AND DELAYED HEALING (15 DAYS OR MORE) IN U.S. SOLDIERS AND GERMAN PRISONERS

Effect of chemotherapy in wounds treated by excision and closure after delay of 11 days or more from original débridement.

	U. S. soldiers					German prisoners				
	Total	Infection	Per cent	Delay	Per cent	Total	Infection	Per cent	Delay	Per cent
All wounds	40	8	20	4	10	33	20	61	10	30
No chemotherapy	10	2	20	1	10	9	6	67	4	45
Oral sulfadiazine	19	4	21	1	5	24	14	58	6	25
Oral sulfadiazine ± Penicillin	30	6	20	3	10	24	14	58	6	25

the entire series, and could be expected to heal well with or without sulfadiazine. In assaying the true effect of chemotherapy, therefore, it is necessary to account for the operation of other variables affecting wound healing and the development of infection.

Two standards of comparing groups of wounds have been utilized, in an effort to compensate for ambiguities or errors inherent in either system.

1. Incidence of infection. To determine the incidence of infection, each wound listed in Table I as having an infectious complication, no matter how trivial, has been tabulated. (Certain of these infections have been designated as serious, either on the basis of constitutional symptoms which they produced, their extent, or their persistence. They are briefly considered as a separate group in Table X.)

2. Incidence of retarded healing. Any wound not solidly healed in 14 days or less has been regarded as delayed in healing. A number of wounds with trivial infections (such as stitch abscesses) were well healed within 14 days. On the other hand, certain wounds without obvious infection were retarded (as in an unhealed drain site, or an indolently healing small separation of the suture line). The advantage of using this criterion as well lies in the fact that in some of these wounds with "technical" delay, the real factor may have been unrecognized low grade infection; furthermore, the best overall guide to therapy in these wounds is the healing time.

In an effort to circumvent the difficulties introduced by the use of both sulfadiazine and penicillin in certain wounds, the following division of the 200 wounds has been made: group A—no chemotherapy, 44 wounds; group B—oral sulfadiazine only at time of secondary closure, 107 wounds; group C—oral sulfadiazine and intramuscular penicillin at time of secondary closure, 36 wounds; group D—oral sulfadiazine with or without intramuscular penicillin at time of secondary closure (group B plus group C), 143 wounds.

TABLE V.—EFFECT OF LOCATION OF WOUND UPON INCIDENCE OF INFECTION AND DELAYED HEALING (15 DAYS OR MORE)

Location	All wounds					All wounds except in German prisoners				
	Total wounds	Infection	Per cent	Delay	Per cent	Total wounds	Infection	Per cent	Delay	Per cent
Buttock and thigh	73	26	36	19	26	49	10	20	9	18
Knee and lower leg	41	8	20	6	15	40	7	18	6	15
Back, chest, abdomen, flank	50	14	28	11	22	41	9	22	8	20
Shoulder and upper arm	19	3	16	2	11	15	3	20	1	7
Forearm and wrist	14	5	36	6	43	12	4	33	5	42
Foot, scalp, perineum	3	1	33	0	0	3	1	33	0	0
Total	200	57	29	44	22	160	34	21	29	18

The 44 wounds in group A are the control group. They are compared throughout with the 107 wounds in group B and also the 143 wounds of group D. Some of the most difficult wounds of the series are to be found in group C, which explains why both agents were given as prophylaxis; this is reflected in the fact that there were 11 infections and 11 instances of delayed healing in these 36 wounds—a much higher incidence than is found in group B. It is therefore unfair to utilize group C as an independent group, but it is also impossible to exclude it from consideration. By running a dual comparison between groups A and B and D, it is possible in group D to account for all infections which developed despite sulfadiazine; in group B, on the other hand (which is roughly comparable to group A), *absence* of infection can be credited to the sulfadiazine alone. In group D the *absence* of infection would be with perfect justification partly attributable to penicillin. In practical application, group A is to be compared with whichever shows the *higher* incidence of infection or delayed healing—groups B or D.

The 10 wounds in which penicillin was the sole prophylactic agent developed 2 infections, and 2 wounds had retarded healing; this group of wounds is used only in analyses of the series as a whole. Three wounds failed promptly, and without evidence of infection from purely technical

TABLE VI.—INCIDENCE OF INFECTION AND DELAYED HEALING (15 DAYS OR MORE) IN WOUNDS GROUPED BY FACTORS ACTING PRIOR TO SECONDARY CLOSURE—GERMAN PRISONERS EXCLUDED

Factor	Total wounds	Infection			Delayed healing		
		Number	Per cent	Significant difference	Number	Per cent	Significant difference
All wounds	159	34	21	—	28	18	—
Cause of wound							
Bullet	36	9	25		6	17	
High explosive	121	25	21	No	22	18	No
Other	2	—	—		—	—	
Type of wound							
Perforating wound	30	9	30	No	8	27	No
All others	129	25	19		20	16	
Size of wound							
Large*	81	21	26	No	15	19	No
Small	78	13	17		13	17	
Time of débridement from injury							
24 hrs. or less	119	28	24	No	21	18	No
25 hrs. or more	40	6	15		7	17	
Chemotherapy at time of injury							
None or questionable	26	9	35	No	7	27	No
Sulfadiazine ± Penicillin	63	14	22		12	19	
Delay—débridement to closure							
10 days or less	91	17	19	No	14	15	No
11 days or more	68	17	25		14	21	
Preparation of wound at general hospital							
7 days or less	125	24	19	No	21	17	No
8 days or more	34	10	29		7	21	

*Large wounds: those 6 cm. or more in length, or 3 cm. or more in width.

causes; 2 from extreme tension and 1 from unobliterated dead space (not a hematoma); these three wounds have been also excluded from comparisons, since the failure was inevitable irrespective of a chemotherapeutic agent.

Tables II and III represent an analysis of the series as a whole from the standpoint of those factors thought most likely to affect the incidence of infection and delayed wound healing. The basic data are not very satisfactory in the category listed as "chemotherapy at time of injury." The data were taken from the individual field records. No account is taken of the duration of the therapy, or of the dosages employed. In some instances perhaps only a single dose was administered. It is possible that some patients did not receive the chemotherapy that the record stated they were given; it is probable that others were given some prophylaxis (since it was Army routine) in spite of the fact that it was not mentioned on the record. In busy forward hospitals, where the highest priority is given to the care of the seriously injured, errors in recording data that have no great bearing on management of the lightly wounded are readily understandable. (Dates of injury and operation, by way of contrast, are very reliable.) Although there is an apparent increase in the incidence of infection in those who received no chemotherapy at the time of injury, and although it is of great importance to determine its value, further analysis in this paper is not warranted. It is of passing interest, however, that what data there are, are in keeping with the conclusions of this study. (This holds true for German prisoners as well, a majority of whom received chemotherapy when injured.)

Factors presenting significant increases in the incidence of both infection and delayed healing are the following: wounds in German prisoners; wounds yielding pathogenic bacteria when cultured at the time of closure; and finally wounds in patients who did not receive oral sulfadiazine at the time of closure. Perforating wounds, delay in closure of the wound or delay in preparing it for closure, closure of the wound by block excision (usually related to delay) and failure to receive

TABLE VII.—INCIDENCE OF INFECTION AND DELAYED HEALING (15 DAYS OR MORE) IN WOUNDS GROUPED BY FACTORS ACTING AT TIME OF SECONDARY CLOSURE OR LATER—GERMAN PRISONERS EXCLUDED

Factor	Total wounds	Infection			Delayed healing		
		Number	Per cent	Significant difference	Number	Per cent	Significant difference
All wounds	159	34	21	—	28	18	—
Anesthetic							
Local	44	13	30	No	9	20	No
General*	115	21	18		19	17	
Number of wounds closed at operation							
Single wound	75	16	21	No	10	13	No
Two or more	84	18	21		18	21	
Aerobic culture of wound at operation							
No pathogenic strains	8	0	0	Yes	0	0	
One or more pathogenic strains	29	10	35		7	24	Yes
All cultured wounds	37	10	27	—	7	19	—
Operative procedure							
Wound excision	59	14	24		8	14	
Wound revision	35	10	29	No	7	20	No
Simple closure	65	10	15		13	20	
Topical sulfanilamide							
Used	31	5	16	No	4	13	No
Not used	128	29	23		24	19	
Wound tension at closure							
Moderate or marked	19	5	26	No	5	26	No
Not significant	140	29	21		23	16	
Drainage of wound							
Wound drained	13	1	8	No	4	31	No
Wound not drained	146	33	23		24	16	
Chemotherapy at time of closure							
No chemotherapy	32	14	44		10	31	
Oral sulfadiazine	82	8	10	Yes	5	6	No
Oral sulfadiazine ± Penicillin	117	18	15		16	14	
Penicillin only	10	2	20	—	2	20	—

*General anesthesia includes two spinal anesthetics.

chemotherapy at the time of the original injury all show significantly increased incidence of infection but not of delayed healing.

The apparent susceptibility of German prisoners to infection demands further investigation. Cross analyses of the principal factors affecting infection in this series with respect to each other (not shown in the paper) demonstrates that in each separate category there still exists a significantly increased incidence of infection in the group of German prisoners as compared with United States soldiers. The most natural assumption to make in connection with poor results in German prisoners, namely, that it is largely due to delay between time of débridement and closure (with resulting block excision of the wound) is refuted by Table IV, which specifically compares the prisoners with United States soldiers on these two counts combined. Whatever the reason for the increase, whether debilitation, faulty nutrition or some other unsuspected cause, it is desirable to exclude German prisoners from further analyses of the effect of prophylactic chemotherapy.

Table V is an analysis of infection and delay cross analyzed by the location of the wounds. When corrected by excluding German prisoners, it can be seen that location is not a factor of much significance in this series.

Tables VI and VII repeat the analyses of Tables II and III excluding German prisoners. Partly because there are fewer cases (and the percentage differences must be correspondingly greater to register as significant) and partly be-

TABLE VIII.—EFFECT OF ORAL SULFADIAZINE ADMINISTERED AT TIME OF SECONDARY CLOSURE; CROSS-ANALYSIS BY FACTORS WHICH TEND TO FAVOR INFECTION AND DELAYED HEALING—GERMAN PRISONERS EXCLUDED

Incidence of infection

Factor	No chemotherapy			Sulfadiazine treated					
				Sulfadiazine only			Sulfadiazine ± Penicillin		
	Cases	Infection	Per cent	Cases	Infection	Per cent	Cases	Infection	Per cent
All wounds	32	14	44	82	8	10	107	18	17
Perforating wounds	8	6	75	14	0	0	18	2	11
Large wounds*	14	10	71	34	4	12	60	10	17
No chemotherapy at time of injury	12	7	58	10	2	20	14	2	14
11 days or more delay from débridement to closure	15	6	40	30	4	13	48	10	21
8 days or more preparation of wound in general hospital	11	4	36	8	3	38	17	5	29
Local anesthesia at time of closure	23	7	30	14	3	21	16	4	25
Procedure Wound excision	16	4	25	24	5	21	38	9	24
Wound revision	7	5	71	13	0	0	26	5	19
Simple closure	9	5	56	45	3	7	53	4	8
Topical sulfanilamide Used	10	3	30	18	1	6	20	1	5
Not used	22	11	50	64	7	11	97	17	18
Two or more wounds closed at operation	8	6	75	43	2	5	68	11	16

*Wounds 6 cm. or more in length, or 3 cm. or more in width.

cause most of the differences are actually less, the only factors which continue to show significant increases in the incidence of infection are the presence of pathogenic organisms in the wound at time of closure, and the lack of prophylactic oral sulfadiazine at the time of closure. However, expected trends in other factors are still discernible although not so marked. It becomes worthwhile at this point to cross analyze these influential factors separately from the standpoint of prophylactic chemotherapy at the time of closure.

In Tables VIII and IX the incidence of infection and delayed healing is considered from the standpoint of those factors appearing to favor their development, as related to the use of oral sulfadiazine. Significant differences are not indicated on these tables, because the break-down produces wound groups with relatively few wounds. It is intended to show a trend, however, demonstrating a lower incidence of infection and retarded healing in the sulfadiazine-treated cases in almost every category. The only groups of wounds which fail to support this trend are those wounds requring prolonged preparation, and those wounds treated either by excision or revision and closure. (This is also demonstrable in Table IV). What there is about these wounds that should cause them to fall outside the general trend is not clear. Further analyses are not enlightening, and it must simply be recorded as a fact.

Table X considers the problem of the "serious" infection. In none of these patients did infection threaten life; but in 18 wounds the infection was definitely more than trivial. There is again seen a sharp increase in the incidence of serious infection in German prisoners, and again an increased incidence in those wounds not treated with prophylactic sulfadiazine. There are insufficient cases to render the difference significant in either prisoners or United States soldiers considered separately, although when they are combined there is a significant advantage for the group which received sulfadiazine.

Table XI is a breakdown of the 73 consecutive wounds which were aerobically cultured at the time of secondary closure. It is unfortunate that all the wounds in the series were not cultured, since the cultured group is not quite representative of the series as a whole (there is a higher incidence of infection than in the entire series). The common pyogenic organisms are considered,

TABLE IX.—EFFECT OF ORAL SULFADIAZINE ADMINISTERED AT TIME OF SECONDARY CLOSURE; CROSS-ANALYSIS BY FACTORS WHICH TEND TO FAVOR INFECTION AND DELAYED HEALING—GERMAN PRISONERS EXCLUDED

Incidence of delayed healing (15 days or more)

Factor	No chemotherapy			Sulfadiazine treated					
				Sulfadiazine only			Sulfadiazine ± Penicillin		
	Cases	Delay	Per cent	Cases	Delay	Per cent	Cases	Delay	Per cent
All wounds	32	10	31	82	5	6	107	16	15
Perforating wounds	8	5	63	14	1	7	18	2	11
Large wounds*	14	6	43	34	2	6	60	8	13
No chemotherapy at time of injury	12	6	50	10	0	0	14	1	7
11 days or more delay from débridement to closure	15	5	33	30	3	10	48	8	17
8 days or more preparation of wound in general hospital	11	3	27	8	1	13	17	3	18
Local anesthesia at time of closure	23	6	26	14	1	7	16	1	6
Procedure									
Wound excision	16	2	13	24	1	4	38	5	13
Wound revision	7	1	14	13	0	0	26	6	23
Simple closure	9	7	78	45	4	9	53	5	9
Topical sulfanilamide									
Used	10	2	20	18	1	6	20	1	5
Not used	22	8	36	64	4	6	97	15	15
Two or more wounds closed at operation	8	5	63	43	3	7	68	12	18
Delay in infected wounds	14	8	57	8	0	0	18	7	39

*Wounds 6 cm. or more in length, or 3 cm. or more in width.

and again the analysis is subdivided according to the nationality of the patient. The numbers are so small that percentages have not been used, but the over-all trend slightly favors the wounds in which prophylactic sulfadiazine was employed. Once more this is less convincing in the group of German prisoners; apparently being a German prisoner had a more decisive effect upon the healing of the wound than any other factor concerned.

Since as many as 5 wounds were closed at one sitting upon a single patient, and since the chemotherapy employed on the patient affected all 5 wounds equally, the objection might well be raised that it is unfair to treat the wounds statistically as separate from the patient. For example, 15 wounds on 3 patients not receiving sulfadiazine might all become infected, and they might all have been the result of three breaks in operating room

TABLE X.—EFFECT OF ORAL SULFADIAZINE ADMINISTERED AT TIME OF SECONDARY CLOSURE UPON INCIDENCE OF SERIOUS INFECTION

	All cases			U.S. soldiers			German prisoners		
	Cases	Serious infection	Per cent	Cases	Serious infection	Per cent	Cases	Serious infection	Per cent
All wounds	187*	18	10	149	10	7	38	8	21
No chemotherapy	44	10	23	32	5	16	12	5	42
Oral sulfadiazine	107	5	5	82	2	2	25	3	12
Oral sulfadiazine ± Penicillin	143	8	6	117	5	4	26	3	12

*10 penicillin treated cases excluded; no serious infection developed in any of these.

There is a significant increase in the incidence of serious infection in the "No chemotherapy" category for all cases, although not for the subgroups of prisoners and U.S. soldiers.

TABLE XI.—INFECTION IN WOUNDS CROSS-ANALYZED WITH RESPECT TO AEROBIC CULTURE AT TIME OF SECONDARY CLOSURE AND PROPHYLACTIC ORAL SULFADIAZINE—73 CONSECUTIVE WOUNDS

	All wounds		No chemotherapy		Oral sulfadiazine		Oral sulfadiazine ± Penicillin	
	Cases	Infection	Cases	Infection	Cases	Infection	Cases	Infection
All wounds	73	33	25	13	44	18	47	21
German prisoners	38	23	12	7	25	15	26	18
U.S. soldiers	35	10	13	6	19	3	21	3
No growth or no pathogens	12	0	6	0	5	0	6	0
Staphylococcus aureus	25	15	9	6	14	7	15	8
Staphylococcus albus	32	15	9	6	22	9	23	9
Streptococcus hemolyticus	8	6	1	1	7	5	7	5
Other streptococci	8	7	6	6	2	1	2	1
Staphylococcus aureus and streptococcus hemolyticus	14	11	5	5	9	6	9	6
U.S. soldier only								
Staphylococcus aureus	11	7	5	4	5	2	5	2
Staphylococcus albus	17	4	5	3	11	1	12	1
Streptococcus hemolyticus	1	1	–	–	1	1	1	1
Other streptococci	5	4	4	4	1	0	1	0
Staphylococcus aureus Staphylococcus albus and all streptococci	6	5	4	4	2	1	2	1
German prisoner only								
Staphylococcus aureus	14	8	4	2	9	5	10	6
Staphylococcus albus	15	11	4	3	11	8	11	8
Streptococcus hemolyticus	7	5	1	1	6	4	6	4
Other streptococci	3	3	2	2	1	1	1	1
Staphylococcus aureus Staphylococcus albus and all streptococci	8	6	1	1	7	5	7	5

technique. This would obviously upset the entire series in a way not shown in the previous tabulations. Table XII deals with the series as *patients* rather than wounds. (A discrepancy of 3 extra patients shown in this table is accounted for by the fact that in 3 cases wounds were closed at two sittings a week or more apart; for the purposes of this analysis the patients were regarded as new patients at the second operation.) An infection developing in any of the patient's wounds causes that patient to be listed under "infection;" similarly with delayed healing. The over-all advantage for the sulfadiazine-treated patients is once more demonstrated as a trend.

The bulk of the cases not treated with sulfadiazine were in the early part of the series. A final objection might be raised that improved results came about as a consequence of better treatment of the later wounds (when experience was greater) rather than from the use of the sulfadiazine. Of the first 75 wounds 30 received no chemotherapy. Infection developed in 13 of the 30 and there was delayed wound healing in 11. Of the second 75 wounds, 12 received no chemotherapy, and in these 12 there was infection in 8 and delayed wound healing in 5. In the last 50 wounds 2 received no chemotherapy with no infection and no delayed healing. Although the majority lie in the first 75 wounds, a high incidence of infection also occurred in those wounds placed later in the series.

Numerous cross-analyses of the data have been made which are not included here. They have all followed the same general trend showing an advantage for wounds treated prophylactically with oral sulfadiazine. It is believed that all the contradictory evidence has been presented.

DISCUSSION

Attention has been drawn to weaknesses inherent in an analysis of this particular group of wounds from the standpoint of the effect of

TABLE XII.—INCIDENCE OF INFECTION AND DELAYED HEALING (15 DAYS OR MORE) IN PATIENTS; EFFECT OF ORAL SULFADIAZINE ADMINISTERED AT TIME OF SECONDARY CLOSURE

Incidence of infection

	All patients			U.S. soldiers			German prisoners		
	Number	Infection	Per cent	Number	Infection	Per cent	Number	Infection	Per cent
All patients	134	44	33	105	26	25	29	18	62
No chemotherapy*	36	16	44	28	11	39	8	5	63
Oral sulfadiazine	73	20	27	53	8	15	20	12	60
Oral sulfadiazine ± Penicillin	92	26	28	71	13	18	21	13	62

*The incidence is significantly higher in the "No chemotherapy" group in U.S. soldiers, but not in the other groups.

Incidence of delayed healing

	All patients			U.S. soldiers			German prisoners		
	Number	Delay	Per cent	Number	Delay	Per cent	Number	Delay	Per cent
All patients	134	38	28	105	24	23	29	14	48
No chemotherapy	36	13	36	28	8	29	8	5	63
Oral sulfadiazine	73	14	19	53	6	11	20	8	40
Oral sulfadiazine ± Penicillin	92	23	25	71	14	20	21	9	43

The differences are not significant statistically
Infection or delayed healing in *any* wound of several on the same patient, places the patient in the appropriate group, although all the other wounds might have healed perfectly. (See text for details.)

prophylactic sulfadiazine. They lie in the small size of the series, and in the fact that therapy was not originally planned as a research project. On the other hand, the series is personal, consecutive, and accurate observations on the fate of each wound are available—a set of circumstances not frequently met with where battle casualties are concerned.

A number of factors affecting wound healing and development of infection have been analyzed. German prisoners were shown to have a high incidence of infection and delayed healing irrespective of other factors, and the bulk of the analysis has therefore excluded them. It has been shown that wounds which were excised and closed, or which had prolonged delay before closure did not appear to have a significant response to prophylactic chemotherapy; the reasons for this are not clear. Wounds in nearly every other category appear to benefit by a course of oral sulfadiazine given prophylactically at the time of secondary closure. The general trend is rendered more significant by the fact that by and large the worst wounds received chemotherapy on empirical grounds in the interest of obtaining the best possible results. (Evidence for this statement is the high incidence of infection and delayed healing in the small group of wounds in which both sulfadiazine and penicillin were employed prophylactically.)

Suggestive evidence that prophylactic chemotherapy at the time of the original injury—days or weeks before the patient reached a general hospital—decreases the incidence of infection after secondary closure, was not pursued because of the likelihood of error in the recordings on the field record of the patients. A consideration of the value of topical sulfanilamide employed at the time of secondary closure is likewise beyond the scope of this paper.

It is recognized that the conclusion in this study is at variance with those of Meleney arrived at in an elaborate statistical study of a much larger series of cases. The two series are not strictly analogous, however. These are wounds produced by the missiles of war, as opposed to wounds incurred through civilian trauma. These are wounds in which closure is delayed deliberately for days or weeks after injury, as opposed to civilian wounds the vast majority of which can and should be closed as soon after the original injury as possible. Finally, these are wounds in patients who have already received, for the most part, some type of prophylactic chemotherapy; perhaps this early chemotherapy inhibits the growth of certain bacteria which lie latent in the

wound until stirred up by operative closure, when they will produce infection unless inhibited again by another course of chemotherapy. Perhaps this early chemotherapy renders the wound more susceptible to infection at later operation than it would have been had no prophylaxis been used at all, and the wound permitted to develop unaided its own local tissue immunity.

CONCLUSION

A personal, consecutive series of 200 secondary closures of soft tissue war wounds is analyzed from the standpoint of the prophylactic effect of sulfadiazine administered orally at the time of closure.

The evidence presented favors the view that sulfadiazine so employed is beneficial, and that it reduces the incidence of postclosure infection and delayed healing.

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THE PELVIC AUTONOMIC NERVES IN THE MALE

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NUMEROUS descriptions of the pelvic plexus of nerves are to be found in the literature. Although some of them are excellent neurologically, none provides serially arranged illustrations prepared from actual gross dissections. In the present article it will be the authors' sole purpose to portray the structure of the pelvic plexus and associated nerves in atlas fashion, with description of related layers and organs.

LITERATURE

Anatomy. According to Davis (1933, 1934), the pelvic plexuses consist of interlacing groups of nerve fibers and of many but extremely small ganglia situated on either side of the ampulla of the rectum. The dimensions of each plexus are said to be 2 by 3 by 1 centimeter. The two plexuses are described as embracing the rectum in the manner in which the levator muscles embrace the anal canal. On each side the plexus is bilaminar, the medial sheet being a continuation of the hypogastric nerve, the lateral a prolongation of branches derived from the sacral nerves. The two hypogastric nerves are joined at a lower level in the pelvis by parasympathetic fibers of the second to fourth sacral segments, these fibers making up the nervus erigens. The two contributions, together with sympathetic fibers from the pelvic chain ganglia, form the pelvic plexus.

The central connections, according to White (1935), are made up of preganglionic fibers from lower thoracic and upper lumbar levels of the intermediolateral columns of the spinal cord. Cells send out axones over the white rami of the lower thoracolumbar outflow to lumbar and preaortic ganglia. Postganglionic neurons originate in sympathetic trunks as well as in preaortic ganglia to form a plexus which descends with the abdominal aorta. At the level of the inferior mesenteric artery are situated two small ganglia which, supplying a circumarterial plexus for branches of the inferior mesenteric artery, ultimately innervate the sigmoid colon and rectum. The remainder of the descending sympathetic fibers form the superior hypogastric plexus in the region of the bifurcation of the aorta. The plexus divides into two plexiform sets of nerves which enter the pelvis, along its lateral wall as the hypogastric nerves (or plexuses).

Pelvic roots, forming the nervi erigentes, arise from medial aspects of the anterior primary divisions of the second to fourth sacral nerves, 1 to 2 centimeters from their foraminous exits. They course to the pelvic plexus, or directly to the rectum. Two or three fine twigs arise from each of the ganglia of the sacral sympathetic chain and enter the posterior border of the pelvic plexus.

The urinary bladder receives sympathetic fibers from the celiac, renal, and mesenteric ganglia, as well as from the first four lumbar ganglia of the sympathetic chain. These fibers, by way of the hypogastric plexuses, and in descent into the pelvis, receive fibers from the last lumbar ganglia, from the inferior mesenteric plexus, and from the superior hemorrhoidal nerve. They also receive fine filaments from the sacral sympathetic chain.

The parasympathetic fibers (from sacral roots), first gathered together as the nervi erigentes, separate into three groups; the upper supplies the fundus of the bladder, the middle supplies the midportion of the bladder, and the lower courses to the inferior aspect, the vesical neck, and the adjacent portion of the urethra.

The cells of origin for these efferent fibers (parasympathetics) to pelvic organs lie in the intermediolateral column of the sacral region. The locations of cell bodies for the afferent fibers are as yet undetermined, but are probably in posterior root ganglia.

The prostate and seminal vesicles receive their innervation from the middle group of fibers while the rectum is innervated by the inferior group, and by some fibers, which, remaining independent of the pelvic plexus, are sent directly from the hypogastric nerve and chain ganglia.

Physiology. The sympathetics, according to Davis (1934) and Meigs (1940), behave as vasoconstrictors and as inhibitors of the musculature of sigmoid colon, rectum, and bladder. They cause ejaculation and contraction of the sphincter of the bladder. Pseudosensory properties are regarded as vasomotor in foundation. The fibers are also glandulomotor to both superficial and deep glands.

The parasympathetics produce vasodilatation and release of the various sphincters. They mediate pain sensation from the bladder. Section of

Contribution No. 444 from the Anatomical Laboratory of Northwestern University Medical School, Chicago, Illinois.

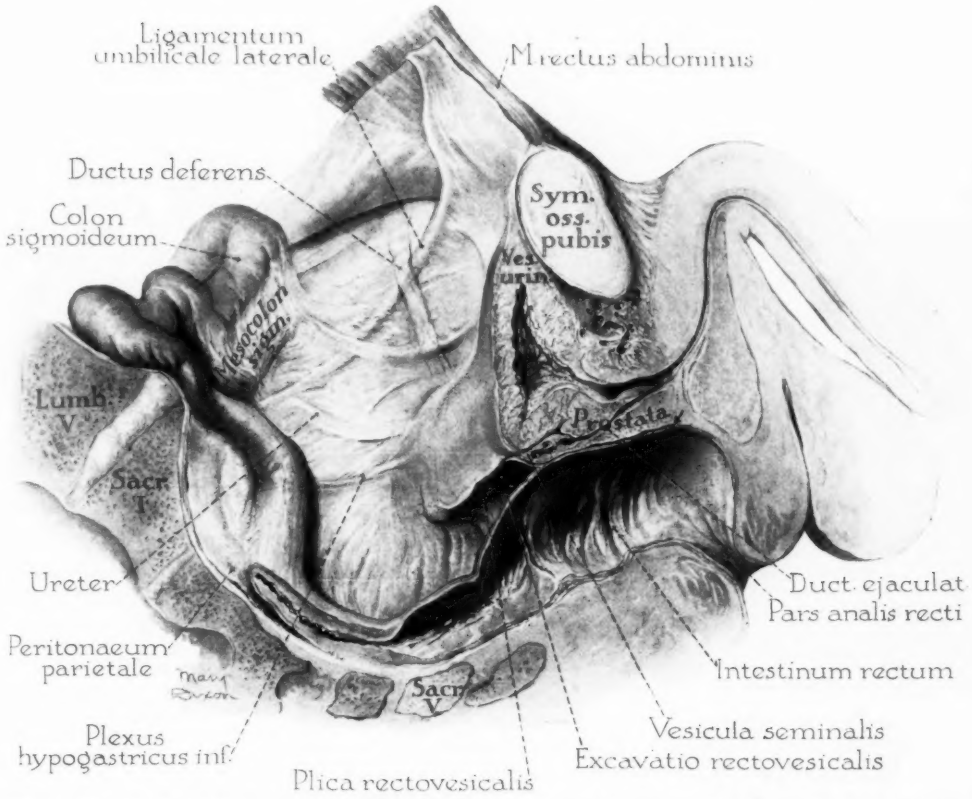

Fig. 1. Topography of the hypogastric plexus and related pelvic structures in a hemisected specimen; peritoneal level (successively deeper levels of same specimen in Figs. 2 to 6). The left half of a male pelvis; peritoneum intact. The section passes through the entire length of the rectum and through the urinary bladder, urethra, etc., and prostate (latter hypertrophied). The section also passes through the interpubic fibrocartilage, seminal vesicles, retropubic plexus of veins, scrotum, and penile cavernous tissue.

the superior hypogastric plexus does not cause atrophy, or disturbance of any motor functions of the bladder; excision of parasympathetics would cause increased blood supply to the pelvis, a lessening of visceral muscle spasm, and interruption of pain impulses to higher centers. Schroeder (1939) quotes McCrae and McDonald (1934) as doubting if either system (parasympathetic or sympathetic) is exclusively excitor or inhibitor; these authors believe the two work together, and with somatic nerves, to regulate bladder function. Yet they are of the opinion that the parasympathetics are more important and that they carry the stronger impulses.

Surgery. Jaboulay (1899) first directed attention to the fact that pain could be relieved by surgery of pelvic sympathetics. Although Latarjet (1913) adequately described the pelvic sympathetics, the first presacral neurectomy was reported by Cotte (1925). Pieri (1926) tried Cotte's operation for relief of pain in tuberculous cystitis; finding the surgery only partly successful; he next excised, with more satisfactory results, the lateral sacral chains at the level of the first sacral segment, and the communicating rami thereof. Learmonth (1930) employed Cotte's method in an attempt to correct neurogenic imbalance of the bladder. More extensive reports were made by Davis (1933, 1934) and Meigs (1940) on the relief of pelvic pain by presacral neurectomy. Schroeder (1939) enumerates several operative procedures for relief of bladder pain: excision of the superior

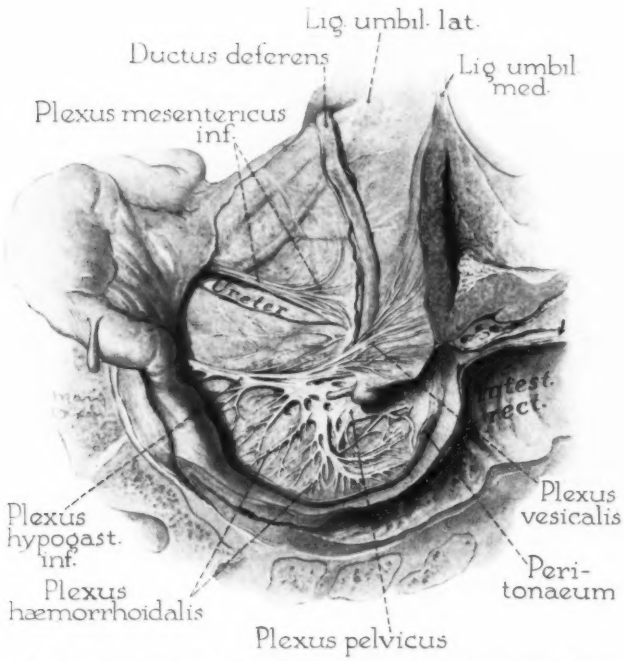

Fig. 2. Topography of the plexuses, ureter, and ductus deferens; immediately subperitoneal level. Showing the structures related to the pelvic colon and rectum, namely, ureter, bladder, ligaments, and nerves. The parietal peritoneum of the lesser pelvis has been removed, and, additionally, the vesical part of the visceral peritoneum. The serous layer remains as the pelvic mesocolon, the covering of the colon and rectum, the rectovesical fascia and also as the bilaminar septum which descends between the bladder and rectum and rectum (fascia of Denonvilliers; marked by arrow here and in Fig. 1). The ureter, ductus deferens, umbilical ligament (obliterated artery) and nerves have been freed from the thin stratum of subperitoneal areolar tissue.

hypogastric plexus; section of the lateral sacral chains; lateral exeresis of the lateral sacral chains; sparing of the somatic portions (pudendal nerve) and parasympathetic fibers, in order to prevent incontinence. Schroeder advocated carrying the dissection, in presacral neurectomy, into the pelvis, in order to reach the lateral sacral ganglia just medial to their foramina.

But no matter what type or degree of excision may come to be favored as a result of further observation on the physiology of the nerves contributory to, or derived from the pelvic plexus, the surgeon will still find it essential to know the form and size of the nerves and plexiform assemblages, and the relation of each to the larger vessels, to the pelvic viscera, to fascial and muscular strata and the more prominent skeletal landmarks. So nebulous is this portion of the conventional anatomical descriptions, that the laboratory dissector rarely finds these highly important structures; by the same token, he knows little about them when confronted by the problems of urological surgery. As mentioned hereinbefore, it is the purpose of the present contribution to make available figures and descriptions which will supplement and amplify those already available in the standard source books.

MATERIALS AND METHODS

The chief specimen used in this study was a well developed male. The dissections were carried out in prearranged serial order. The main illustrations (Figs. 1 to 6) are direct pictorial records of the laminar antomy of the pelvic wall, autonomi

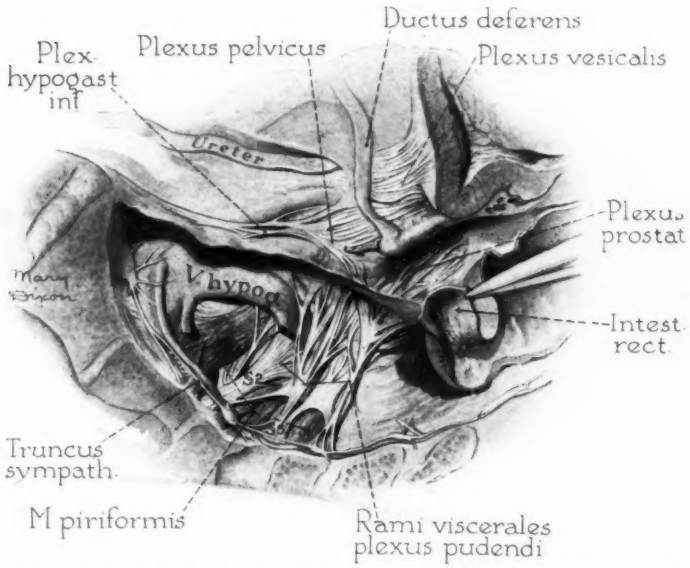

Fig. 3. Relation of the hypogastric plexus to the terminal vesical plexus, and to the deeper rami derived from the sacropudendal plexus. The latter are situated at parietal level. Depicting the rectum, urinary bladder, ductus deferens, ureter, pelvic autonomic nerves, and related structures. The following have been removed: pelvic colon; proximal part of rectum (distal segment retracted); superficial leaf of autonomic nerves to the point of severance of the rectum (opposite fifth sacral vertebra). The nerves are followed toward the rectovesical excavation; the ductus deferens is mobilized as far as its point of junction with the seminal vesicle, where the associated nerves lie within the rectovesical fold. The hypogastric and gluteal veins are exposed. The sacral sympathetic chain, with communicating fibers from the second to the fourth sacral, is exposed, as is also the subjacent piriformis muscle. The layers shown are in succession: hypogastric and pelvic plexuses lodged chiefly in subperitoneal areolar tissue; heavy retroperitoneal connective tissue, upon which the visceral branches of the above named plexuses rest or through which they pass; visceral rami of the sacropudendal plexus of nerves; musculature (piriformis, passing from the sacrum through the greater sciatic foramen).

nerves, and related structures; they were prepared at life size.[1] An accessory illustration (Fig. 7) reduces the nerves to a schema. The diagrammatic sections (Figs. 8 and 9) are based upon a coronally cut pelvis of a second male specimen. Between the prostate gland and the rectum it descends as a partially fused plate of tissue, termed Denonvilliers' fascia (arrow, Fig. 1).[2]

OBSERVATION AND DISCUSSION

Peritoneum. The peritoneum is elevated by: the obliterated hypogastric (umbilical) artery, slightly, by the superior vesical branches derived therefrom, and by the ductus deferens and ureter (Fig. 1).

[1]Comparable strata in the female pelvis were illustrated in an earlier article (Figs. 1 to 4; Curtis, Anson, Ashley, and Jones, 1942).

[2]The reader is referred to the excellent article on Denonvilliers' fascia by Tobin and Benjamin in an earlier volume of this journal.

The rectovesical fold is prominently tall; it is little more than apposed layers of peritoneum, projects 1 centimeter backward from the bladder; the excavation which it guards is 1.5 centimeters deep, measured from the edge of the fold to the depths of the rectovesical excavation. The transverse vesical fold is but a slightly elevated part of the peritoneum. The lateral umbilical fold has a maximum height of 1.5 centimeters (at the pubic crest); the fold is flattened so that its space opens lateralward.

The pelvic colon possesses a mesocolon which is 6 centimeters long where the colon reaches the midline over the fourth lumbar vertebra (Fig. 1); the mesentery becomes gradually shorter, being 2 centimeters long in the true pelvis opposite the first sacral vertebra; fixation occurs at the level

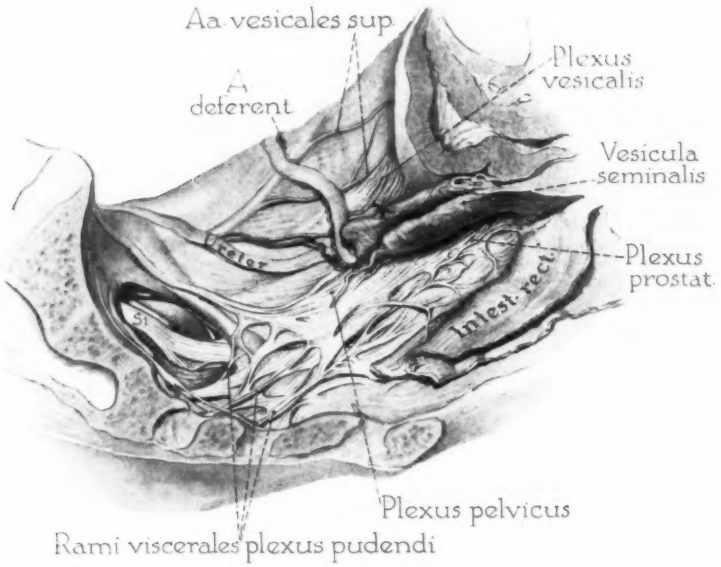

Fig. 4. Form and composition of the deeper leaf of nerves. Showing the pelvic plexus, the superficial leaf of which has been entirely removed to expose the deep layer of the pelvic autonomic plexus and the nerves contributing to its fabric. The nerves from the second to fourth sacral (erigens) remain intact, and the anterior continuation of the pelvic autonomic plexus has been followed ventralward to the bladder, seminal vesical, and prostate. The rectum, transected at coccygeal level, has been retracted. The large vein which overlay the first sacral nerve (in Fig. 3) has been removed. The superficial group of vessels is exposed (superior and middle vesicular arteries from the obliterated hypogastric); the deep vessels (hypogastric and external iliac) remain covered by the heavy lamina of pelvic fascia. The main mass of the plexus is parietal in position, resting upon tissue which, in turn, lies immediately upon the obturator fascia.

of the ridge between the second and the third sacral segments. The pelvic colon is constricted through the greater part of its length. The rectum is similarly constricted as it lies in front of the third and fourth sacral pieces; it widens slightly in front of the fifth, and further enlarges as it passes distalward beyond the area of vertebral relationship. The narrowed anal canal leaves the rectum at an angle of almost 90 degrees. The three portions of the tube are, then, related to one another as the parts of a letter Z reversed.

Subperitoneal structures. The heavier retroperitoneal tissue which ascends on either side of the urinary bladder as a wing, to iliac level, in projecting backward forms the plate of tissue over which the peritoneum is draped to produce the rectovesical fold (Fig. 2).

The observations on the general arrangement of subperitoneal tissue are in accord with those made earlier on the female (Curtis, Anson, and Beaton, 1940). Vessels in the category of the hemorrhoidals are lodged in a fine areolar layer which is immediately subperitoneal; autonomic nerves coursing to viscera are next in level, becoming more superficial as they approach the organs; parietal vessels are placed in the heavy connective tissue which is clearly "parietal," and with them are situated visceral rami; most deeply placed, and actually retrofascial, are the elements of the sacral and lumbar plexuses, from which latter communicating rami are sent through the heavier retroperitoneal tissue to reach the autonomic plexuses near the bladder and rectum.

The ductus deferens, ureter, and accompanying nerves lie within a thin areolar layer with the middle hemorrhoidal and associated sympathetic plexus (which give off rectal, vesical, and prostatic sets of nerves). Still covered by tissue of areolar character, but evident as elevations, are the "obliterated" hypogastric artery (lateral umbilical ligament) and its derived superior vesical

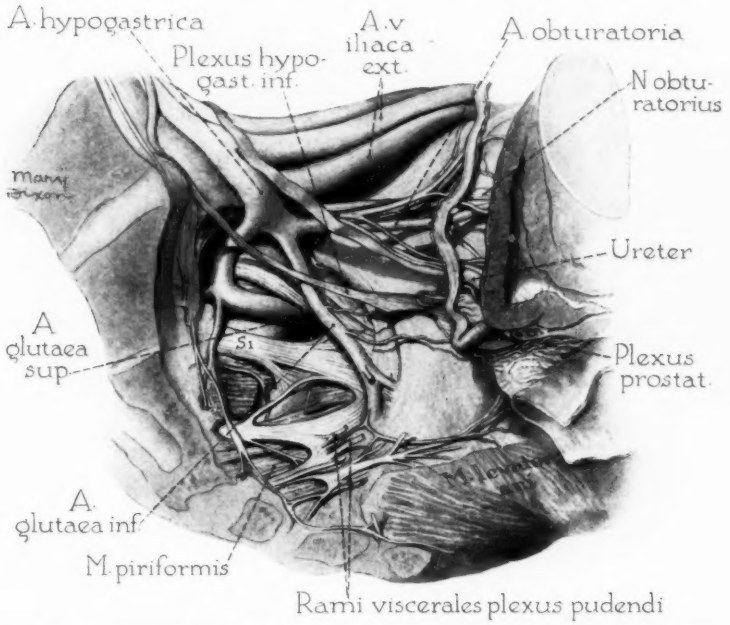

Fig. 5. Parasympathetic origin of the rami contributory to the pelvic plexus, and deep structures related to the latter. The deep relations of the pelvic plexus, shown by removal of the plexus and the heavy retroperitoneal tissue which partially invests it. The transected parasympathetic nerves (visceral rami of the pudendal plexus) remain connected with the sacral plexus; the distal continuations of the autonomics have been cut as they disappear beneath the prostate and seminal vesicle. The connections between the inferior hypogastric plexus and the pelvic plexus have been severed along the inferior margin of the former. All of the retroperitoneal connective tissue has been removed, exposing the endopelvic fascia, the vessels and nerves to the pelvic viscera and parietes, and to the lower extremity. The connective tissue has been removed from the greater sciatic foramen to expose the full course of the nerves contributory to the sacral and pudendal plexuses and the larger vessels as they leave the pelvis. The superior fascia of the pelvic diaphragm has been removed, exposing the levator ani muscle.

branches. The outlines of the gluteal, obturator, middle hemorrhoidal and pudendal vessels are masked by the heavy retroperitoneal layer.

Nerves. Most important is the position of the several sympathetic plexuses (Fig. 2; cf. Fig. 7). They are parietal in position; they do not immediately surround the organs, as familiar textbook illustrations would lead one to believe. Actually, the large middle hemorrhoidal is actually 5.5 centimeters distant from the rectum; it sends numerous rami to the rectum, these passing posteriorly over an area bounded by the line at pelvic mesocolic attachment (above) and the line projected (below) from the superior surface of the urinary bladder. In the erect body their direction would be horizontal, while that of the trunk from which they are derived would be vertical.

The deeper structures are chiefly related to the nerves of the intermediate and deep "leaves" (Fig. 3). The intermediate leaf consists of the parasympathetic fibers of the second, third, and fourth sacrals, and sympathetics which enter these just lateral to the chain ganglia. The parasympathetics (nervus erigens) intercommunicate, forming a small plexus, which makes up a deep leaf. The two layers meet approximately 3 centimeters lateral to the rectum. Some of the fibers of the parasympathetic derived from the fourth sacral diverge medially to enter the wall of the rectum. The intermediate leaf is separated from the deep (sacral plexus) by the large hypogastric vein and its gluteal tributary. The vein in turn crosses the piriformis muscle obliquely. From the large ganglion resting upon the lateral surface of the body

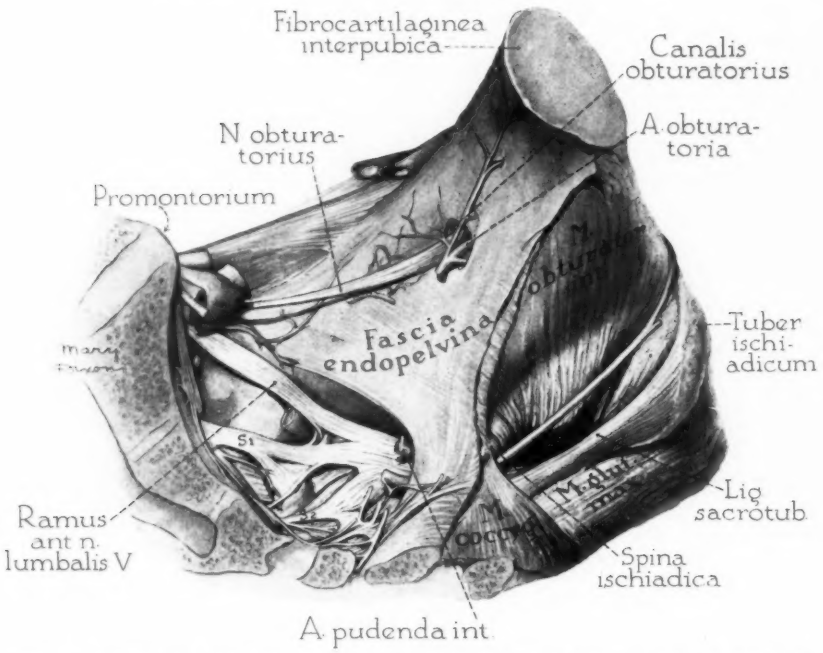

Fig. 6. Sacral plexus with derivative parasympathetic fibers (cut), and parietal and related diaphragmatic muscles and fasciae. Viscera and autonomic plexuses have been removed. The greater portions of the larger vessels have also been removed, leaving only their proximal and distal ends. The obturator nerve is exposed throughout its course. The sacral plexus has been followed to its point of exit through the greater sciatic foramen (i.e., to point of convergence of the trunks to form the sciatic and pudendal nerves). The connective tissue has been removed from the foramen to demonstrate its depth. The parietal portion of the endopelvic fascia is fully exposed; the levator ani muscle has been cut close to its origin along the tendinous arch, where the levator fibers are shown by trimming away the superior fascia of the pelvic diaphragm. The ischiorectal fossa has been freed of fat to reveal the pudendal artery (other associated vessels and nerves removed), obturator internus muscle, sacrotuberous ligament, and gluteus maximus muscle.

of the first sacral vertebra many small fibers course over the sacral artery and hypogastric vein to supply these vessels; some reach, and supply, the hypogastric artery and its branches. From each of the ganglia a gray ramus communicans may be seen passing deeply through the substance of the piriformis muscle to the sacral nerve of its corresponding segment. The deep leaf of nerves consists mainly of the second, third, and fourth sacral nerves. At their points of emergence from the bony foramina, the second is 0.5 centimeter wide, the third is 0.4 centimeter, and the fourth is 0.3 centimeter in width. A distance of 1.5 centimeters separates the second from the third, 1.3 separates the third from the fourth. The height of the "arch" (measured transversely) between second and third is 2.0 centimeters, that between third and fourth is 1.3 centimeters. At the point of union of the three components the band is 2.5 centimeters wide (measured vertically).

The configuration of the Frankenhaeuser plexus and its components becomes clear when the superficial leaf of nerves has been removed (Fig. 4; cf. Fig. 7). The sympathetic nerves from superior and lateral origins form the inferior hypogastric plexus, or hypogastric nerve; they are joined by the small plexus formed by the parasympathetic nerves from the second to fourth sacrals. The two systems then blend into a single large flat band overlying the deep vessels from the hypogastric. The shape is that of a large Y, the sympathetics forming the lateral arm, the parasympathetics, the medial. The fusion of the two continues as one large flat sheet, composed of many nerve fibers and sheaths of connective tissue. The fibers course toward the prostate, bladder, and upper

urethra to innervate those structures. There is a separate group of small fibers which passes into the region of the seminal vesicle. Some fibers detach themselves from the plexus to supply the terminal portion of the rectum.

The superiorly located fibers of the plexus pass beneath the seminal vesicle and the crooked portion of the ductus deferens to enter the wall of the bladder. The lowermost, as previously mentioned, enter the rectum, and intermediate fibers continue to the prostate and membranous urethra.

The distance from the mid-point of the plexus to the lateral rectal wall is 3.5 centimeters. The length of the Y-shaped plexus is 8 centimeters (to the nerves at the prostate).

The parasympathetic nerves are five in number (Fig. 5, severed at the point of entrance into the plexus). The cranial two arise from the junction of the second and third sacrals; the third arises from the third sacral, the fourth nerve from the fourth sacral entirely, and the fifth from the junction of the third and fourth. The plexus is prolonged between the rectum and prostate; the plexus was previously described as an intermediate group of nerves leaving the plexus and entering the prostate, the inferior aspect of the bladder, and the seminal vesicles. The inferior, or caudal, group of nerves leaves the plexus to enter the ampulla of the rectum, as three or four stems of gross dimensions.

Vessels. The hypogastric artery and its branches and corresponding veins lie deep to the fascial layers which house the autonomic nerves (Fig. 5). The most superiorly placed vessels are the external iliac artery and vein. Next is the umbilical artery with its four vesical branches, all of which course first toward the superior surface of the bladder, some then passing to the inferior. The vesical arteries are lodged in an intermediate layer of connective tissue which covers the deep vessels and remains entirely separate from them. The small deferential artery takes origin from the lowermost of the vesical arteries; the ureteric artery, also in this layer, arises from the small vesicular branch just above the one which gives origin to the deferential. Another small artery passes directly through the plexus to enter the tip of the seminal vesicle. The obturator arises by a common stem with the umbilical; the gluteals, descending, leave the pelvis above and below the piriformis muscle. The inferior gluteal artery gives rise to the internal pudendal just before it leaves the pelvis.

The vessels are internal to the endopelvic fascia (Figs. 5 and 6).

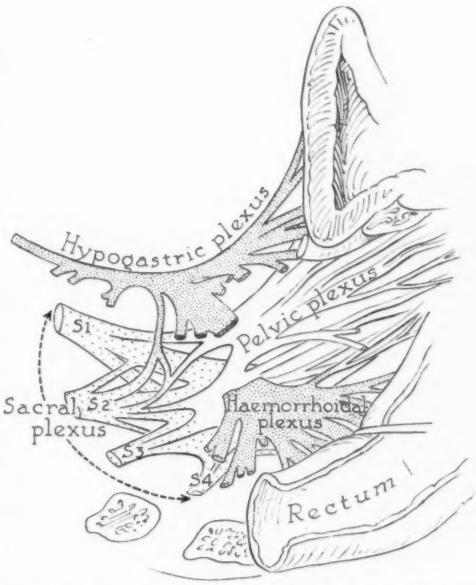

Fig. 7. Diagram of the pelvic plexus, showing origin and distribution of the chief components, and their gross interrelationships. Medial aspect. The hypogastric plexus is shown intact in its curving course to the urinary bladder, but has been cut away in that part which, overlying the pelvic plexus, contributes to the hemorrhoidal plexus. Between these two, and lateral to them, the fibers derived from the sacral nerves are shown streaming toward the bladder, prostate, anal canal, rectum, etc.

The endopelvic fascia. The so-called endopelvic fascia is actually aponeurotic in nature. Continued upon the levator ani and coccygeus muscles the endopelvic fascia becomes diaphragmatic fascia (Fig. 6). Over the upper part of the obturator internus muscle it is parietal, and when reflected from the pelvic diaphragm to the rectum and bladder it becomes visceral (cf. figures in Curtis, Anson, and Beaton, 1940).

It is clear, then, that the relations to fascial levels are of fundamental importance. In the heavy retroperitoneal layer is located the large pelvic plexus, with its vesical and prostatic continuations (Fig. 4); into this layer sink the originally superficial fibers of the inferior hypogastric plexus (Fig. 2), and to it ascend the visceral rami originating from the sacral plexus of nerves (Figs. 3 to 5). In dissections this set of relationships is strikingly demonstrated when the heavy stratum is reflected (Fig. 3); as they enter the pelvis from above the sympathetic fibers are situated just beneath the serous layers and upon the heavy

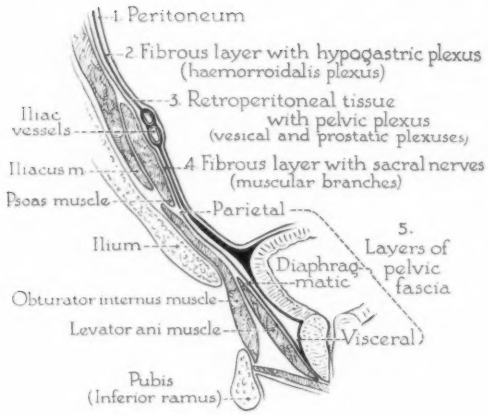

Fig. 8.

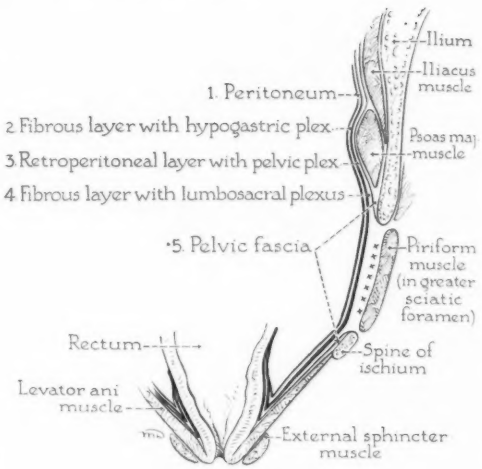

Fig. 9.

Figs. 8 and 9. Diagrams of the location of autonomic nerves, showing relations of the main sets to the subserous strata of the pelvis. Coronal sections in anterior view. The chief elements of the broad pelvic plexus are lodged in the heavy layer of retroperitoneal tissue (at level *3*), the hypogastric plexus and its subsidiaries are situated in a thinner layer internal or medial thereto (level *2*), while the sacral plexus and its fibers to pelvic musculature are located external or lateral to retroperitoneal layer (at level *4*). Posteriorly, at the greater sciatic foramen its nerves (at site of crosses in Figure 9), contributing chiefly to the formation of the sciatic nerve, rest upon the fascial covering of the piriformis muscle.

retroperitoneal layer; on the contrary, the parasympathetics, originating behind, are located beneath the heavy layer and upon the endopelvic fascia as the latter covers the parietal musculature (obturator internus). All of the fibers from these two sources which ultimately reach the urogenital organs enter, and course through the heavy retroperitoneal layer; this would be the expected arrangement, since the strong fibrous layer becomes the immediate coat of each of the pelvic organs, merging with the sheath derived from the endopelvic fascia.

Sciatic foramen. The sciatic foramen is bounded anteriorly by the arching border of the endopelvic fascia. Through it passes the superior gluteal, inferior gluteal, and internal pudendal arteries, and the lumbosacral nerves which converge to form the sciatic. The parasympathetic nerves (nervus erigens), also visible, arise just before the sacral trunks join. The most caudal of the nerves arising from the sacral plexus is the nerve to the levator ani.

Ischiorectal fossa. The visceral rami derived from the sacropudendal plexus are, then, prominent as a group where they leave the sacral nerves at the arciform border of the sciatic foramen (Figs. 5 and 6). But, within the ischiorectal fossa, comparable fibers to the erectile bodies are difficult to segregate; they tend to follow, inconspicuously, the pudendal nerve.

The ischial spine constitutes the serviceable landmark; around it the obturator internus disappears as it leaves the pelvis; attaching to the ischial spine are the posterior end of the iliococcygeus part of the levator ani, and the lateral insertion of the coccygeus muscle which forms the posterior fourth of the pelvic diaphragm.

CONCLUSIONS

The autonomic nerves of the pelvis make up a set of neural sheets which not only are of gross dimensions, but which are of such position and form as to be demonstrable in the form of subperitoneal bands with predictable relationships to bony landmarks, to large blood vessels and to viscera. The large bands and the lesser contributory fibers, as they course from root or plexus of origin to area of visceral termination, are either lodged within readily dissectable fibrous laminae or situated at levels either immediately superficial or deep to such laminae.

The chief layer is that which is most marked as it extends upward along the pelvic wall after having formed a strong sheath for the urinary bladder and associated structures. It is the layer which transmits, also, the blood vessels of visceral supply. Resting upon this stratum, at subperitoneal level, is an areolar tissue in which is situated most of the nerves of supply to the rectum; under the same stratum are placed the sacropudendal plexus

and the rami which pass therefrom to the large plexus in the intermediate layer. The intermediate is, therefore, the chief one of the three; into the pelvic plexus which it contains pass rami from the sympathetic and parasympathetic plexuses in layers on its internal and external aspects.

In the superficial (internal) layer of areolar tissue course the hypogastric plexus, that portion of the pelvic plexus which sends rami chiefly to the rectum, the contributory mesenteric plexus, and the ductus deferens. These are structures which are subperitoneal or were originally mesenterial (when, embryonically, a mesorectum existed). Being placed immediately beneath the serous lining of the pelvic cavity, they elevate the peritoneum—but less markedly than do the umbilical ligaments (Fig. 1).

Topographically, the inferior mesenteric plexus lies anterior to the ureter, following it closely; the inferior hypogastric plexus and its pelvic prolongation lie posterior to the ureter, between the latter and the rectum. The main mass of the plexus courses in a curving line—concave anteriorly—between the first piece of the sacrum and the rectovesical fold.

In its distal portion the fibers spread out principally on the superior surface of the bladder; behind, groups of fibers radiate to the rectum, a strong set forming a secondary plexus close to the rectal wall. Altogether, these plexuses and derived fibers of visceral supply cover a semicircular area whose posterior boundary follows the contour of the rectum and that of the sacrum against which the latter rests (Fig. 2).

Embedded in the heavy layer of true retroperitoneal tissue are the deeper elements of the autonomic supply (Fig. 4). The anterior boundary of this set of fibers coincides with that of the more superficially situated hypogastric plexus, but its form is strikingly different. It assumes the configuration of a broad ribbon, wider at the proximal and distal ends than in the middle two-fourths of its extent. Its widest portion is proximally situated, where visceral rami are contributed by the sacral nerves (Figs. 3 and 4); upon it converge, distally, the fibers of the vesical portion of the pelvic plexus, to produce a second broadening; terminal distribution to the bladder, prostate, seminal vesicles and rectal ampulla is also instrumental in causing the widening of the band which occurs at its anteroinferior end. In an anteroposterior direction this intermediate band is somewhat more extensive than the superficial; the former is carried to the sacrum (the points of origin of the nerves, Fig. 4), the latter to the rectum (the visceral area of supply, Fig. 2). The intermediate band is the longer of the two, owing to the fact that the greater bulk of its fibers are supplied, not to the rectum in the sacral curve, but to the bladder, prostate, anal canal, as these rest upon the pelvic floor.

The third and deepest of the three neural strata is that composed of the proximal portions of the visceral rami of the pudendal plexus and the sacral plexus, from which the rami are derived. Because the branches quickly enter the pelvic plexus—merging, on the latter's deep aspect, and within the substance of the heavy retroperitoneal tissue—this third layer is but slightly longer than it is wide. It overlies the second to fourth nerves (from which it arises); being thus caudally placed, its long axis is at almost a right angle to that of hypogastric plexus in the superficial, or first, layer. The upper cords of the sacral plexus, and the lumbosacral cord from the abdominal level, rest in similar tissue upon the piriformis muscle; the pudendal rami leave the nerve trunks near the point where the latter emerge through the greater foramen en route to the gluteal region. As the rami course toward the pelvic plexus, they come to lie upon the fascia covering the obturator internus.

The sympathetic fibers which descend into the pelvis from abdominal level form the mesenteric and hypogastric plexuses; the parasympathetic fibers, commonly described as forming a nervus erigens, enter the pelvic plexus as a set of anastomotic nerves. All fibers, so far as gross examination reveals, are mixed in the broad ribbon of nervous tissue which is termed pelvic plexus. Therefrom fibers stream toward the several pelvic organs, a degree of stratification obtaining in the distribution to mesenterial and to retroperitoneal viscera: for the most part, nerves to the rectum pass, on immediately subperitoneal, or superficial, level, from the anterior border of the plexus backward, in radiating fashion, to the pelvic portion of the digestive tube; similarly, nerves to the urinary bladder, subjacent prostate gland, to the seminal vesicles, lodged, at the intermediate level in the heavy sheath of retroperitoneal tissue, stream downward and forward to the organs named—all ultimately supported by the funnel-shaped pelvic diaphragm.

From the surgical standpoint, the following conclusions seem warranted: sympathetic fibers may be transected by presacral neurectomy, parasympathetic elements left untouched by the same procedure; in both abdominal and perineal approach to the rectum (in high operation for carcinoma) the chief portions of the autonomic plexuses are removed, by safe distance, from the

surgical field—being parietal in position in the dorsal portion of the pelvic cavity; in any of the regular approaches (pubic, transsymphysial, perineal, or rectal) to the urinary bladder or prostate gland the disturbance of tissue would occur in areas where concentration of autonomic fibers is minimal—behind the main plexiform aggregations in anterior approach, and above them in inferior entrance to the pelvis. However, in wide removal of carcinomatous lymphatic and associated fibrous tissue within the pelvis, the areas where nerves are abundant would be affected; the plexuses, in resting upon the hypogastric artery and its important branches, are situated between the peritoneum and the lymphatics, since the latter are closely associated with the blood vessels.

In summary, then, it may be said that the nerves of supply to the pelvic organs are so disposed as to be naturally protected from damage in urological surgery. In spreading out upon the bladder from behind and above, terminal fibers are fewest on the anterior (apical) and inferolateral portions; in supplying the rectal and anal parts of the canal, the nerves do not descend with the tube in the form of an investing net, but, approaching the canal from the side, they end in relation to local segments. Finally, it may be pointed out that so great is the intermingling within the plexus of fibers derived from various sources, that localized excision or extirpation would be expected to result in relatively slight interference with function of a pelvic organ.

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STUDIES ON EXOPHTHALMOS PRODUCED BY THYROTROPIC HORMONE

II. Changes Induced in Various Tissues and Organs (Including the Orbit) by Thyrotropic Hormone and Their Relationship to Exophthalmos

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IN a preceding publication (21) the development of exophthalmos in thyroidectomized animals receiving various preparations of thyrotropic hormone was described. Antuitrin T produced a striking degree of exophthalmos but in many animals it also produced profound myasthenia and loss of weight in spite of the absence of the thyroid. A so called purified preparation, however, failed to produce exophthalmos, toxic manifestations, or loss of weight but did cause some hyperplasia of the thyroid of intact animals. A crude thyrotropic preparation which was prepared in a manner similar to that of the so called purified preparation but without the additional efforts at purification and which was administered in quantities equal in thyroid-stimulating effect to the purified product, caused exophthalmos. This exophthalmos, however, was less striking than that produced by antuitrin T. Toxic effects and loss of weight from the crude preparation were minimal. The specific metabolic principle, a fraction of thyrotropic hormone, did not produce exophthalmos and was known from the work of others (8,18,19) not to produce thyroid hyperplasia.

The tissues of these animals, from which accurate data on exophthalmos have been obtained, have furnished the source of material for this report.

LITERATURE

In 1936 Smelser (43) described an infiltration of a stainable material, accompanied by nests of lymphocytes and edema, in the extraocular muscles and orbital fat of guinea pigs rendered exophthalmic by thyrotropic hormone. This was confirmed by Paulson (37,39) who also described loss of striations in the extraocular muscles. Smelser (44,46) concluded in later papers that the changes in muscle were confined to the connective tissue between the muscle fibers. Paulson (38,39) later found muscle degeneration and round cell infiltration in cardiac and other skeletal muscles. He reported that this change was most striking in the first few days of administration of thyrotropic hormone and that it occurred regardless of the presence or absence of the thyroid. The cellular reaction was found to a much milder degree in normal and thyroidectomized control animals.

Aird (1,2) demonstrated varying degrees of cellular reaction in extraocular muscles and edema of orbital tissue with several thyrotropic preparations. Brock (13), although primarily interested in cellular infiltration in cervical sympathetic ganglia, mentioned the feature in muscle. Smelser (44) and Paulson (37) reported that the muscle changes might not be present although exophthalmos developed. Paulson (38) could not demonstrate an appreciable increase of the water content of muscles but in agreement with Smelser (44-47) he did show an increase of the water content and volume of the orbital tissue mass.

Smelser (45), after finding an edematous infiltration in the connective tissue of fat in the orbit, studied other fat depots. Cervical and axillary fat were unaffected but the fat about the kidneys, ovaries, and ureters appeared to be involved by the same process although to a much less striking degree than in the orbit. These observations on fat depots other than the orbit have not been confirmed. Since the investigation described in this publication was carried out, Smelser (47) has described an increase of the residue of the orbital tissues after the extraction of fats and water in animals that have been given thyrotropic hormone.

The significance of the cellular reaction elicited by thyrotropic hormone in fat, connective tissue, and muscle is not understood. Just what the relationship of these tissue changes may be to the exophthalmos that develops is not certain. A cellular reaction accompanied by edema and fibrosis in orbital tissues of patients suffering from

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Dr. Dobyns, Fellow in Surgery, Mayo Foundation.

Fig. 1. Left, perinephric fat from normal control guinea pig. Right, perinephric fat from guinea pig treated with antuitrin T. Note the apparent replacement of opaque fat by a more transparent gelatinous material (transillumination ×10).

malignant exophthalmos has been described by Naffziger and many others (11,12,15-17,22,23, 27,31,32,33-36,43,44,48). It may be of interest that Haik (27) recently reported "extreme fatty metamorphosis of the liver" and cloudy swelling in the kidney in a case of malignant exophthalmos at necropsy. Naffziger (34), reporting on muscle biopsies from locations other than the orbit, did not observe the muscle changes usually encountered in the orbit.

EXPERIMENTS PRELIMINARY TO THIS STUDY

In preliminary experiments, examination of tissues of animals receiving antuitrin T confirmed these reports of the presence of round cells in orbital tissue, to a lesser degree in muscles, and in many of the fat depots throughout the body. In other preliminary studies it was found that these cells contained many fine droplets of fat. Likewise muscle fibers throughout the body and the cells of the liver and the kidneys were loaded with fat droplets after thyrotropic hormone had been administered.

PURPOSE OF THIS STUDY

The purpose of this study was to investigate the possibility of a general systemic cellular reaction in guinea pigs given antuitrin T and to correlate these reactions with those known to occur in the orbit, associated with exophthalmos. In addition, observations were made of the reactions which ensued in animals when they were given various other crude and so called purified thyrotropic preparations. Since the unit potencies of these preparations differed from that of antuitrin T, any comparison of their effectiveness with that of antuitrin T was not undertaken.

METHODS

The several groups of animals that had received various thyrotropic preparations for varying lengths of time were as follows:

A. Antuitrin T was administered in daily amounts containing 25 Junkmann-Schoeller units[1] to 15 thyroidectomized animals, 7 of which had also been orchectomized. Four intact animals also received this product. The period of administration was from 3 to 32 days.

B. The solvent for antuitrin T, including the preservative but without the pituitary ingredient, was given in comparable daily doses as a control to 4 intact animals.

C. Five intact animals with comparable body weights were fasted, to induce a loss of weight like that sustained by some of the animals receiving antuitrin T. These served as controls for changes sustained solely from loss of body weight.

D. A so called purified thyrotropic factor was given to 8 thyroidectomized animals in daily amounts containing 2.5, 5.0, and 10.0 Rowlands-Parkes units[2] for periods of from 7 to 39 days.

E. Crude thyrotropic preparation was given in daily amounts containing 5 and 10 Rowlands-Parkes units to 10 thyroidectomized animals for periods of from 8 to 24 days.

F. The specific metabolic principle, which is a fraction of a thyrotropic preparation and which failed to produce thyroid hyperplasia, was administered in daily amounts of 1 cubic centimeter (later raised to 2 cubic centimeters) to 4 thyroidectomized animals for periods of 6 to 8 days.

Most of the animals were killed by ether. As a control procedure, a few animals were killed by lethal doses of pentobarbital sodium. Axillary, cervical, periureteral, orbital, and testicular fat and temporal, cardiac, and extraocular muscles were removed and fixed in 10 per cent solution of formalin. The entire orbital contents were dissected from the bony orbit as a single unit. This mass of tissue was fixed and sections were made through the entire substance just posterior to the globe so that a cross section of all retrobulbar tissues was obtained. Sections were made of the liver, kidney, spleen and representative lymph

[1]A unit is that amount of hormone which, injected daily for three days, causes in 2 of 3 animals (28,29), recognizable hypertrophy of the epithelium and disappearance of colloid in the thyroids of guinea pigs 100 to 150 gm. in weight. (Potency was based on assay by manufacturer.)

[2]A unit is that amount of extract which given daily for 5 days will cause the thyroids of miniature female guinea pigs weighing 200 grams to double their weight or attain a weight of 60 milligrams. Normal thyroids were described as weighing approximately 30 milligrams (42). (Potency was based on assay by manufacturer and confirmed by the author.)

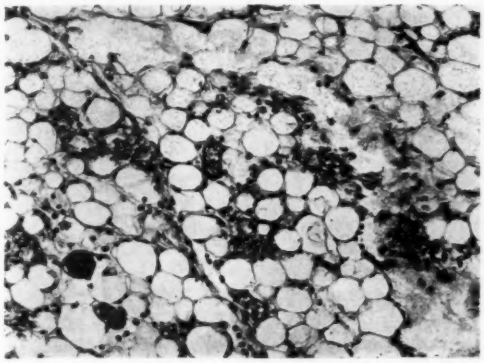


Fig. 2. Changes induced in the testicular fat tab of a thyroidectomized guinea pig by 0.5 cubic centimeters of antuitrin T daily for 3 days (hematoxylin and eosin ×118).

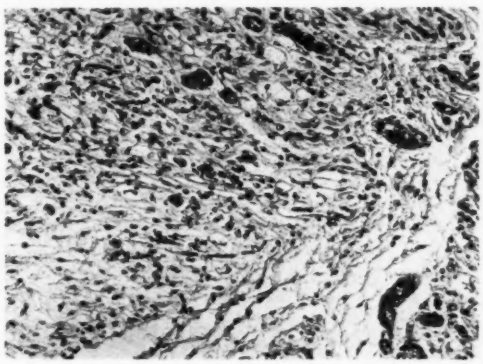


Fig. 3. Changes induced in the testicular fat tab of a thyroidectomized guinea pig by 0.5 cubic centimeters of antuitrin T daily for 13 days (hematoxylin and eosin ×118).

nodes. In some animals sections of the ureter and of the small intestine were prepared.

Two techniques for histologic preparation were employed. Frozen sections were cut and stained with scarlet red and counterstained with hematoxylin. Paraffin sections were stained with the routine hematoxylin and eosin stains. In instances in which connective tissue changes were observed, Mallory-Heidenhain and van Gieson stains were applied. In some instances mucicarmine stains were used.

At the time of thyroidectomy and orchectomy, biopsies were taken of cervical and testicular fat. These tissues were subsequently contrasted with those obtained from the same animals after thyrotropic hormone had been given to them.

The changes in each tissue were studied and recorded by grading the degree of change on the basis of 1 to 4 (1 being the smallest discernible change and 4 being the most striking degree of change).

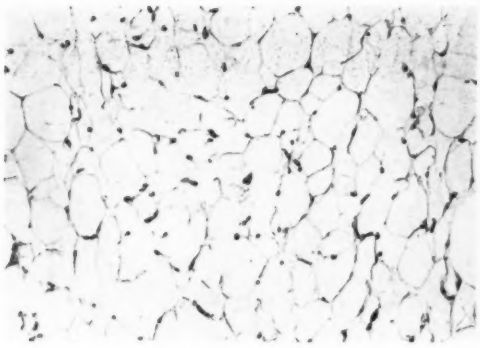
RESULTS

A. Gross changes induced in tissues by thyrotropic hormone preparations. Antuitrin T produced the most striking gross changes in animals regardless of the presence or absence of the thyroid. Fat from most of the fat depots had a redder appearance and possessed a more firm and rubbery consistency than did fat of normal animals. This gross change was most striking in the first few days of administration of antuitrin T. After longer periods the fat depots were extremely depleted of fat, and, in the place of the fat, there was found a translucent gelatinous material (Fig. 1). The most striking changes in fat occurred in animals which had lost the most weight. Although some of the animals treated with antuitrin T had lost considerable weight, in many cases the volume of the gelatinous fat depots was not materially decreased. This was in contrast to the markedly decreased volume of the fat depots of the fasted control animals which had lost comparable amounts of weight. In the fasted guinea pigs which had lost considerable weight and possessed depleted fat depots, the fat remained soft and showed little if any of the gelatinous character. The fat in animals which were given the preparations, other than antuitrin T, did not differ grossly from the normal.

In animals which had received antuitrin T for only a few days the skeletal muscles were rather pale and had a tendency to tear easily when stretched. The livers of such animals were extremely pale, slightly enlarged, and very friable. But after more prolonged administration of antuitrin T, the skeletal muscles and liver returned to a more normal color and consistency. Color changes similar to those in the liver were induced in the kidneys.

In the animals given antuitrin T, the connective tissue septa of the harderian glands were edematous and appeared as dark partitions between the lobules, much in contrast to these septa in normal glands.

In the animals which received the crude thyrotropic preparation the connective tissue septa of the harderian glands were less edematous than those in animals receiving antuitrin T. In certain of this group which gained less weight, the livers were rather pale and mottled and the fat depots were abundant, occasionally more glossy and edematous than normal.



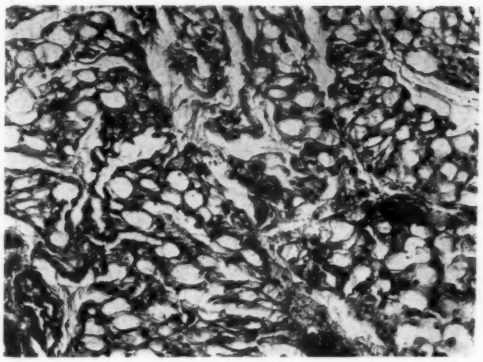
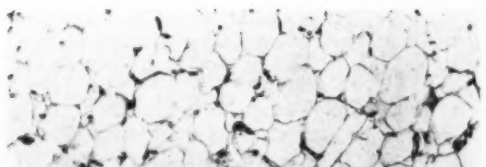


Fig. 4. a, left, Axillary fat of normal guinea pig. b, Changes induced in the axillary fat of a thyroidectomized guinea pig by 0.5 cubic centimeter of antuitrin T daily for 13 days (hematoxylin and eosin ×118).

The tissues of the animals which received the solvent for antuitrin T and of those which received the so called purified thyrotropic factor or the specific metabolic principle did not show any of these gross changes such as occurred in the animals receiving antuitrin T or the crude thyrotropic preparation.

B. Microscopic changes induced in tissues of animals receiving antuitrin T. The most consistent change observed in the tissues of animals receiving antuitrin T was the appearance of large numbers of mononuclear and polymorphonuclear leucocytes containing fat droplets, a condition not ordinarily seen in such cells of control animals. This cellular reaction was accompanied by varying degrees of edema. These fat-containing cells occurred not only in the orbital tissue but throughout the connective tissue generally. Fat tissues throughout the body were markedly altered (Figs. 2, 3, 4, and 5). The thin septa of connective tissue fibers between the fat cells were three to four times their normal thickness. Clusters of large and small mononuclear and polymorphonuclear leucocytes had infiltrated into these thickened septa. In some areas where the reaction was extreme, a homogeneous, faintly staining material had formed within these connective tissue spaces to such an extent that the fat cells appeared to be floating in a matrix (Figs. 2 and 4). This cellular reaction resembled very closely the histologic pattern of the reparative processes seen in fat necrosis accompanying traumatized tissue.

In animals given antuitrin T for short periods, there were more polymorphonuclear cells containing more fat droplets and there was more edema but only slight proliferation of connective tissue. In animals given this preparation for



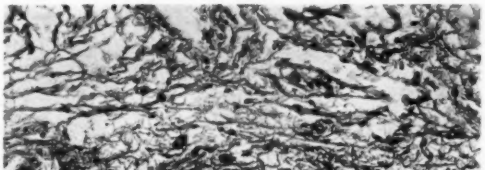


Fig. 5. a, left, Orbital fat of normal guinea pig. b, Changes induced in the orbital fat of a thyroidectomized guinea pig by 0.5 cubic centimeter of antuitrin T daily for 9 days (hematoxylin and eosin ×118).

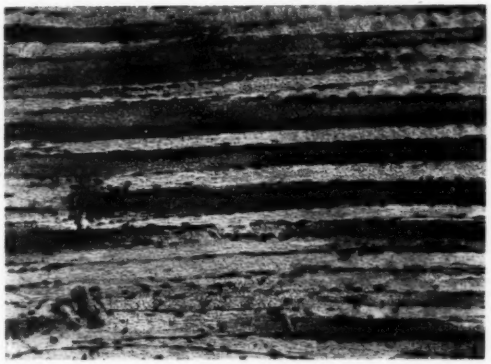


Fig. 6. Fat laden skeletal (temporal) muscle fibers of an intact guinea pig that had received 0.5 cubic centimeter of antuitrin T daily for 2 days (scarlet red and alum hematoxylin ×96).

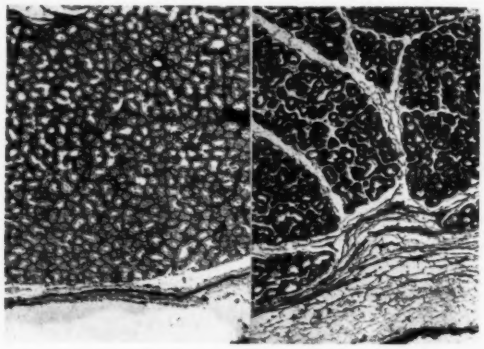


Fig. 7. a, left, Normal harderian gland (×35). b, Marked edema of the connective tissue around and within the harderian gland of a thyroidectomized guinea pig in which exophthalmos had been induced by administration of antuitrin T (×35).

longer periods, there were fewer polymorphonuclear cells, more lymphocytes, more large macrophages and fibroblasts and more collagenous connective tissue but less edema.

In sections of the cardiac and skeletal muscles of injected animals there was but little cellular infiltration, although there was more than in sections of normal muscle. In preparations stained with hematoxylin and eosin a mild degenerative process of muscle fibers, characterized by a loss of striations and a granular appearance of the fibers, was evident. This occurred in a spotty manner without apparent relation to the blood supply or to any other recognized anatomic feature.

These changes in muscle took on added significance when fat stains were applied to these same muscles, for it was found that the fibers, in the same spotty fashion, were loaded with tiny droplets of fat (Fig. 6). In some sections of a single fiber the fat was in great abundance while in other places along the same fiber relatively little change from the normal was found. The degree of change in various muscles in the same animal showed considerable variation. The extraocular muscles when studied in this way were almost always found to contain more fat than any other muscles. At times, the lymphocytes and the large macrophages were more abundant about those portions of the muscle containing the most fat; however, in other instances the most affected muscles contained no new cellular elements. These macrophages and lymphocytes were always most abundant in connective tissue bordering muscle fibers or in perivascular locations.

The same general trend of the reaction that was observed in connective tissue and fat; namely, less fat in tissue macrophages as treatment continued, occurred also in muscle tissue. Animals treated for a short time contained much more fat in the muscle fibers than those treated for longer periods. A very close correlation was noted between the presence of fat in the muscle fibers and the degree of myasthenia produced by antuitrin T. This correlation held true even in the animals

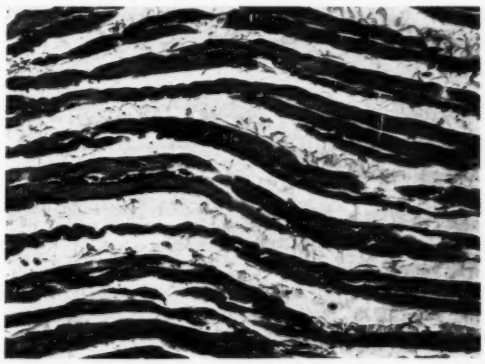


Fig. 8. Edema in skeletal (temporal) muscle following the administration of 0.5 cubic centimeters of antuitrin T daily for 13 days to a thyroidectomized guinea pig (hematoxylin and eosin ×140). This is an example of a striking degree of edema in muscle. There was rather high-grade edema of connective tissue (see Figs. 3 and 4) throughout the body of this animal as well as marked exophthalmos. The temporal muscle was chosen because by its position edema is least likely to develop on the basis of dependency.

treated for longer periods when fat in muscle was rarely found and myasthenia was infrequently observed.

The large, pale, friable livers observed in the animals receiving antuitrin T for a short time contained relatively large amounts of fat, but the livers of those animals given the preparation for longer periods contained less fat. In those animals in which the kidney was studied the droplets of fat were present in cells of the tubular epithelium. However, here again the amount of fat present was readily correlated with the duration of the injections and corresponded well with the presence of fat in muscle and in liver. Fat droplets were seen, too, in the large reticuloendothelial cells of the lung, in the spleen and in lymph nodes of animals which possessed pronounced changes in fat elsewhere in the body. Likewise the epithelial cells of the ileum and bronchi contained tiny droplets of fat in their cytoplasm. Excessive quantities of fat were found in the lacteals of the small intestine.

Edema in the orbit was most easily recognized in the septa of the harderian glands (Fig. 7). It was present, too, in the connective tissue of the fat in the orbit (Fig. 5) and in other fat depots of the body (Fig. 3). In a few animals which had had striking exophthalmos, extensive edema had developed in the temporal muscle (Fig. 8). In many animals edema was either present in small amounts or absent entirely from these muscles.

The infiltration of a homogeneous, faintly staining, intercellular substance in connective tissue, especially in adipose tissue, appeared quite consistently, not only in the orbit but elsewhere in the body (Figs. 2, 3, 4, and 5). Mucicarmine stains did not reveal the presence of mucin but van Gieson and Mallory-Heidenhain techniques indicated that this material was probably collagen of young connective tissue. This homogeneous material was associated with the cellular reaction described previously and was usually most prevalent after a period of treatment, when the acute phase of the cellular reaction was subsiding. The effect of antuitrin T on the tissues of intact animals is the same as seen in thyroidectomized animals when one considers equal periods of treatment. The general impression was that the edema that developed in normal animals was somewhat less than that in thyroidectomized animals.

The tissues of the group of animals which received the solvent for antuitrin T did not sustain these histologic changes. This, therefore, would seem to eliminate the possibility that the solvent or preservative was the causative factor in producing the tissue changes. Exophthalmos, it will be recalled, did not develop in this group of animals.

Because the most striking changes in fat occurred during the early administration of antuitrin T and because it was during this period that the animals lost the most weight, it seemed advisable to know whether phagocytosis of fat occurred in animals which lost weight rapidly for other reasons, for example, fasting. It is known that fasting is accompanied by a rapid mobilization of fat from depots and that this fat is subsequently found in abundance in the liver.

In the fat depots of fasted animals, in which the fat was extremely depleted, nuclei of fat cells persisted and there was a relative increase of connective tissue with few lymphocytes, macrophages, and polymorphonuclear leucocytes. Fat droplets were occasionally seen in these cells but in negligible amounts when the fasted animals were compared with animals which had received antuitrin T. In no instance was this finding more than minimal in the fat depots of fasted animals.

The presence of fat in muscles was also found in fat-stained preparations from fasted animals but to a very mild degree. There was also a slight amount of edema in the connective tissue of some of the fasted animals.

It has been shown by the author in experiments described elsewhere (20) that thyroidectomy alone was not followed by any appreciable increase of cellular elements or edema in connective tissue.

C. Microscopic changes induced in the tissues by other thyrotropic preparations. The purified thyrotropic factor, in the amounts administered, resulted in the appearance of some fat in the liver but no increase of cellular elements in connective tissue was recognized and phagocytosis of fat by such cells was not graded more than 1. In the hematoxylin and eosin preparations there was some evidence of an increase of the number of macrophages but the deposition of new connective tissue was not demonstrable. Muscle degeneration, however, occurred to an appreciable degree (grade 3) in only one animal, which was an exception and in which some exophthalmos had developed. Edema in all tissues including the orbit was more noticeable than in thyroidectomized controls, and a very slight increase in connective tissue had been induced.

Generally speaking, the tissue reaction in the animals given the crude thyrotropic preparation, in the amounts indicated, was less pronounced than that found in animals given antuitrin T. However, it was more marked than the equivocal

changes induced by the so called purified thyrotropic preparation. The degree of edema in these animals resembled that of animals treated with antuitrin T and occurred throughout all the connective tissues examined. There was an abnormal increase of the number of tissue macrophages but polymorphonuclear cells were rarely seen. The presence of fat droplets in tissue macrophages, however, was considerably less than in animals given antuitrin T. In only about a half of the animals such intracellular fat was not demonstrable; however, it was relatively marked in a few animals which had gained less weight. The appearance of fat droplets in muscle fibers was moderate in most animals. It was not demonstrable at all in one animal, which was not conspicuously different in other respects. The abnormal presence of fat in other organs was variable and the homogeneous faint staining material was not found in these animals.

In animals which received the crude thyrotropic preparation in the amounts indicated, less striking exophthalmos developed than in animals treated with antuitrin T. Edema of connective tissue was a prominent feature but the cellular reaction associated with the abnormal presence of fat in many locations and the deposition of connective tissue was not as striking. The shortest period of observation of the animals was 8 days and on the average these animals were observed longer than were those given antuitrin T. The experience with antuitrin T has shown that the acute phase of the reaction occurred early in the course of administration of thyrotropic hormone. The presence of moderate numbers of mononuclear cells in the tissue of animals treated for longer periods with the crude thyrotropic preparation may bear witness to a more acute reaction that had preceded.

The tissues of the animals which had received the specific metabolic principle in the amounts indicated were of interest because in most instances they appeared to be unchanged. One animal which had lost some weight because of apparent toxicity of the product had a grade 3 edema in the orbit but this was not found in other tissues, and the animal had not become exophthalmic. In some animals very small amounts of fat were demonstrated in muscle fibers.

COMMENT

This report is specifically concerned with certain changes which were observed in the orbit and in various other regions and organs of guinea pigs and which ensued on the administration of antuitrin T for varying periods. In addition, it includes brief reference to results obtained in comparable animals on the administration of certain other preparations, including the solvent for antuitrin T, a crude, and a so called purified thyrotropic preparation, the potencies of which had been assayed in terms of units not comparable to those of antuitrin T. Since antuitrin T was assayed on the basis of one type of unit and the crude and purified preparations were assayed on the basis of another type of unit, it is not possible to compare the effectiveness of these preparations with that of antuitrin T on the basis of unit potency. It is however, possible to relate the exophthalmos to the tissue changes in any one animal or in any group of animals, irrespective of the preparation which produced the changes.

As hitherto shown (21), antuitrin T produced marked exophthalmos. The crude thyrotropic preparation, in the amounts administered, was less effective and the purified thyrotropic preparation, in the amounts given, was least effective of all in producing exophthalmos. The degree of cellular reaction, the edema and the connective tissue changes which occurred in these three groups of animals were most marked in those receiving antuitrin T, less so in those receiving the crude preparation, and least so in those receiving the so called purified product.

This study has shown that a general systemic alteration in fat depots occurred in animals which received antuitrin T. These depots were rapidly depleted of their fat contents, which were replaced by a more translucent, gelatinous material. These changes were associated with the infiltration of large numbers of polymorphonuclear leucocytes and tissue macrophages which were loaded with tiny fat droplets. The impression was gained that these large macrophages had phagocytosed fat and were transforming into fibroblasts still containing fat, and ultimately gave rise to connective tissue fibers. Much edema was associated with this reaction. Further evidence of the changes in the fat of the body was shown by the appearance of large amounts of fat in the liver, kidney and skeletal and cardiac muscle and in the epithelium of bronchus, ureter, and the ileum.

It is probably of considerable clinical interest that a relationship was recognized between the appearance of fat in the skeletal muscles and the profound myasthenia that developed in animals shortly after antuitrin T was given. These cellular reactions as well as exophthalmos occurred in animals regardless of the presence or absence of the thyroid or the testes. In the animals in which there was the appearance of fat in abnormal quantities in the foregoing tissues,

droplets of fat were also observed in the reticuloendothelial cells of the lungs, lymph nodes, and spleen. It would seem that the appearance of fat in these specialized cells constitutes a part of the same generalized systemic reaction throughout the body. The results of these experiments suggest that there is a generalized alteration of fat metabolism and that the connective tissue reaction and the exophthalmos may be associated with it.

These observations confirm the opinion of Smelser (45) that tissue reactions may occur in other locations than the orbit. The degeneration of skeletal muscle fibers, illustrated with the hematoxylin and eosin preparations described by Paulson (37), was apparently due to the presence of fat in these muscle fibers. Whether the lymphocytes and macrophages in muscle described by him as well as others are present to remove the fat or to carry away products of cellular degeneration is unknown.

The demonstration of these cytologic changes in tissues, resulting in the ultimate deposition of connective tissue in the involved regions, supports the opinion of Friedgood (24-26) and Aird (1,2) that exophthalmos, after being maintained for a period, becomes irreversible. This also supports the observation of Smelser (47) that there is an increase of the residue which remains after the extraction of water and fat from orbital tissues of animals treated with thyrotropic hormone.

It is well known that pituitary extracts cause an increase of liver fat (3-7,10,30). Barrett, Best, and Ridout (5) showed by labeling fat molecules that fat was transferred from the various depots to the liver. But the possible relation of this observation on the liver to conditions which incite exophthalmos has not been suggested.

Several terms have been given to unisolated substances in the anterior pituitary which influence the mobilization of fat, but their chemical relationship or similarity to the substances which stimulate the thyroid gland is uncertain.

The fact that fasted animals show some of these tissue changes, especially those relating to fat metabolism, confuses somewhat an interpretation of the mechanism of such reactions to antuitrin T. The changes produced by the hormone are not identical with those induced by fasting. Furthermore, they are far more extreme than those seen in the fat depots of fasting animals. It has been pointed out (21) that thyrotropic hormone had toxic effects on animals even before the thyroid response was fully elicited. It is known that animals, when given thyrotropic hormone, do not withstand surgical procedures well (14). In a similar manner fasting animals (49) or animals recovering from surgical procedures (21) do not well withstand the administration of thyrotropic hormone.

The observations of increased fat in the epithelium and lacteals of the small bowel of these animals receiving antuitrin T may have some relation to the observation of Rony and his associates, who found an increase of fat in the lacteals of fasted animals. In a similar way the observation by Binet and his associates of fat globules in the bronchial epithelium and round cells of the lung in fasting animals is recalled by these observations, which show the presence of fat in the bronchial epithelium of animals receiving thyrotropic hormone.

It is quite possible that there may be some relationship between the myasthenia produced in these animals and the myasthenia in exophthalmic goiter. Plummer and Wilder found a positive correlation between the loss of quadriceps strength and the exophthalmos in exophthalmic goiter. These systemic changes may in some way be related to the exophthalmos and to the myasthenia produced in animals by administration of antuitrin T.

SUMMARY

Tissues of animals which during life had been given various thyrotropic hormone preparations and on which very accurate records of the development of exophthalmos had been made were studied grossly and by several histologic techniques.

Antuitrin T, which produced the most striking exophthalmos, was found to produce gross and microscopic changes in connective tissue not only in the orbit but elsewhere in the body.

The study showed that as a result of the administration of thyrotropic hormone there was a generalized alteration in fat depots, which are rapidly depleted of their fat contents and are replaced by a more translucent gelatinous material. Histologically these changes in fat and connective tissue are characterized by the presence of edema and the infiltration of large numbers of polymorphonuclear leucocytes, lymphocytes, and tissue macrophages. Early in the reaction the polymorphonuclear leucocytes and tissue macrophages are loaded with tiny droplets of fat. Later an increase of new connective tissue is evident. This reaction was correlated with the exophthalmos which had previously developed in these animals.

Skeletal and cardiac muscle fibers during the early period of administration of thyrotropic

hormone lost their striations and were found to contain multitudes of tiny fat droplets, which lined up in a pattern representing the cross-striations of the fibers. New cellular elements were present among muscle fibers. Considerable significance was attributed to a close correlation between the presence of fat in the muscles and the myasthenia present in these animals before death, a fact which may have clinical correlations.

Further evidence of alterations in fat during the early administration of thyrotropic hormone is the presence of large amounts of fat in the liver, kidneys and epithelium from several locations, as well as large phagocytic cells of the lungs, spleen and lymph nodes.

These changes took place regardless of the presence or absence of the thyroid.

Since the completion of this investigation there has appeared in the literature a study by Pochin on exophthalmos in guinea pigs, some of which is confirmatory and some contradictory of the results of the present study.

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EDITORIAL

SURGERY
Gynecology and Obstetrics

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MAY, 1946

THE USE OF COMPRESSION IN THE TREATMENT OF INJURIES

THE use of compression to arrest and prevent escape of blood and serum into body tissues represents a surgical principle which, to use Homans' words, has been "perennially discovered, discredited, forgotten, rediscovered and reaffirmed."

The subcutaneous rupture of blood vessels and the rapid escape of blood and serum into soft tissues are of frequent and everyday occurrence. The blow over the eye or forehead, the crushing of a finger tip, the twist of an ankle—all lead to rapidly forming swelling and the subsequent discoloration that indicate blood vessels have been torn and blood has infiltrated the surrounding tissues. Severe contusions and crushing injuries of soft tissue and bone are followed by the same train of events in a more exaggerated form.

When one is confronted with an open wound from which active bleeding is taking place one's first instinct—whether layman or surgeon—is to apply pressure to stop the bleeding. The surgeon in the operating room almost daily, instinctively and logically, presses gauze sponges or "laparotomy pads" against a bleeding surface to arrest oozing. The same principle can be employed, and with almost equal effectiveness in the control of bleeding which does not meet the eye as a rapidly welling pool of blood, but which is accumulating under the surface in direct ratio to the extent of injury and the elasticity of the overlying tissues.

When one recalls what happens when a considerable quantity of blood infiltrates soft tissues—the harmful compression of fragile living cells, the slow disintegration of red cells, the fibrosis that follows the absorption of serum and disintegrated corpuscles—it becomes a matter both of logical treatment and of importance to arrest such bleeding as promptly as possible. When one recalls further that after an extensive crushing injury the loss of blood into the soft tissues can be so great as to lead to shock and threaten life, the arrest of such hemorrhage becomes a matter of life and death. The most certain means at our command of controlling such bleeding is by smooth firm compression of the affected area.

There is a second important group of cases in which similar conditions obtain—those in which blood without red cells escapes rapidly into the surrounding tissues and leads to the same local and general symptoms of swelling, distention of tissues and fluid loss. Whatever the cause of the fluid loss that rapidly follows exposure to extremes of heat and cold—increased permeability of damaged capillaries,

local vasodilator reaction which "causes the region (surrounding a burn) to become an open shunt with capacity to contain a maximal amount of intravascular blood"[1] or whether still other factors at work—every worker interested in the treatment of burns or of injuries due to freezing has been concerned with the rapid loss of fluid into the tissues and with the serious effect of such loss, both on the tissues at the site of injury and on the entire body mechanism. With the concentrated attention that has been given to these injuries in recent years it has become increasingly apparent that the prompt application of pressure over the injured area is the most certain and effective means of preventing and checking fluid loss, and of arresting the "white hemorrhage" which is so important a factor in the clinical picture that develops rapidly after severe injuries due to extreme heat and cold.

A third group of cases in which the use of compression is an important factor in bringing about recovery is well illustrated by a simple case report from Sampson Gamgee's *Surgical Lectures*, published in 1883.[2]

"On the 18th September, 1879, a bloated, middle-aged man came before me in the out-patient room, with his right leg big, tense, purple, and exquisitely tender.

"The man had earned his living as a hawker, and had been a hard drinker. On admission, the right leg was of greatly increased size, and of deep purple colour; the skin tense and shining, and intensely sensitive to the slightest touch. Circular measurement of the two legs gave the following result:

	Right	Left
At the middle of the patella....	18½ inches	17 inches
Six inches below.....	18 inches	17 inches
Round the malleoli.....	14 inches	11¼ inches

"Placing the man on his back and raising the foot, I enveloped the limb in a layer of cotton wool, over which I constructed a compressing millboard and bandage latticework.

"September 19th, 9 a.m.—After the lapse of 13 hours, bandages very loose from the considerable subsidence of swelling which has taken place in the twelve hours since they were applied. I applied another bandage with firmer pressure, and suspended the limb. The patient had passed a comfortable night, with the exception of some pain between midnight and 5 a.m. He is now perfectly comfortable.

"8:15 p.m.—Has been very easy all day. On removing the apparatus the limb is much paler and softer, and scarcely tender on pressure. The patient's spontaneous expression is, 'It is wonderful how I can bear it handled now, and I could not stand a feather touching it last night.' The following are the circular measurements of the right leg:

		Decrease in 24 hours
Mid patella.....	17 inches	1½ inches
Six inches below.....	15¾ inches	2¾ inches
Round the malleoli.....	12 inches	2 inches

"The strips of pasteboard were now re-moistened, to fit the shrunken limb, and bandaged to it, latticework fashion, over cotton wool with increased pressure. The application last night, though conducted most gently, caused occasional exclamations of intense suffering, but the patient bore it tonight, though executed comparatively roughly, without the least pain. The same process was repeated daily, to follow up the decreasing limb with equable pressure; and at the end of a week, the two legs were of equal size.

"Admitting the beneficial influence of the horizontal position of the body, and of the suspension of the limb in the flexed position, there can be no question that the immediate relief of pain and the rapid subsidence of swelling were chiefly due to smooth elastic pressure."

Gamgee cites a number of similar cases in which disabilities resulting from widespread exudation through the soft tissues associated with a chronic inflammatory process responded rapidly to the application of compression and immobilizing splints. Furthermore, he points out that many English, French, and German writers during the century preceding had repeatedly emphasized the importance of compression in the treatment of injuries and of chronic inflammation —a method "forgotten, rediscovered and reaffirmed." Ironically, perhaps, Gamgee obtained such good results by adhering to sound surgical principles that he was reluctant to accept the teachings of his friend and classmate, Lister.

It seems almost superfluous to repeat in a surgical journal Blair's emphasis on "The

[1] Glenn, Wm. W. L., Gilbert, Helen H., and Drinker, Cecil K. J. Clin. Invest., 1943, 22: 609.

[2] Gamgee, Sampson. On the Treatment of Wounds and Fractures. 2d ed. London: J. & A. Churchill, 1883.

Influence of Mechanical Pressure on Wound Healing"[1] but a few lines deserve repetition because so much of good surgical sense is compressed in them.

"There are chiefly four basic things to be gained by the use of properly applied mechanical pressure to wounds:

"The elimination of dead spaces.

"The control of oozing.

"The limitation of venous and lymph stasis.

"Limitation of the amount of plastic material that pours into the wound."

[1]Blair, V. P. The influence of mechanical pressure on wound healing. Illinois M. J., 1924, 46: 249-252.

Fowler of the University of Minnesota said at a recent meeting in Minneapolis that an understanding and appreciation of the value of compression was one of the outstanding lessons learned during the war. Perhaps it has been so well learned that it will not again have to be "rediscovered and reaffirmed."

SUMNER L. KOCH.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

HOSPITAL CARE OF THE SURGICAL PATIENT; A SURGEON'S HANDBOOK WITH AN APPENDIX ON THE TREATMENT OF WOUNDS. By George Crile, Jr., M.D., and Franklin L. Shively, Jr., M.D. Foreword by Evarts A. Graham, M.D. Springfield, Illinois: Charles C Thomas, 1946.

AN INTRODUCTION TO ESSENTIAL HYPERTENSION. By Richard F. Herndon, M.D., F.A.C.P. Springfield, Illinois: Charles C Thomas, 1946.

ANATOMY OF THE HEAD AND NECK. By R. T. Hill, Ph.D. Philadelphia: Lea & Febiger, 1946.

BURMA SURGEON RETURNS. By Gordon S. Seagrave, M.D., Maps by Phoa Lieng Sing and Lucas Manditch. New York: W. W. Norton & Co., Inc., 1946.

DIGITALIS AND OTHER CARDIOTONIC DRUGS. By Eli Rodin Movitt, M.D. New York: Oxford University Press, 1946.

MODERN ANAESTHETIC PRACTICE. Edited by The late Sir Humphry Rolleston, B.T., G.C.V.O., K.C.B., M.D., F.R.C.P., and Alan Moncrieff, M.D., F.R.C.P. 2d ed. Published on behalf of *The Practitioner*. London: Eyre and Spottiswoode (Publishers) Ltd., 1946.

NURSING AND NURSING EDUCATION. By Agnes Gelinas, R.N., A.M. New York: The Commonwealth Fund, 1946.

MEDICINE IN INDUSTRY. By Bernhard J. Stern, Ph.D. New York: The Commonwealth Fund, 1946.

NURSING IN COMMERCE AND INDUSTRY. By Bethel J. McGrath, R.N. New York: The Commonwealth Fund, 1946.

AFECCIONES VASCULARES QUIRURGICAL DEL ENCEFALO. By Alfonso Asenjo, F.R.S., F.A.C.S., and Enrique Uiberall. Santiago: Central de Publicaciones, 1945.

NEUROSYPHILIS. By H. Houston Merritt, A.B., M.A. (Hon.), M.D., Raymond D. Adams, M.A., M.D., and Harry C. Solomon, B.S., M.D. New York: Oxford University Press, 1946.

NOTABLE NAMES IN MEDICINE AND SURGERY. By Hamilton Bailey, F.R.C.S. (Eng.), F.I.C.S., and W. J. Bishop, F.L.A. London: H. K. Lewis & Co. Ltd., 1946.

JOURNAL OF THE HISTORY OF MEDICINE AND ALLIED SCIENCES. Vol. 1, No. 1. New York: Henry Schuman, 1946.

PENICILLIN THERAPY AND CONTROL IN 21 ARMY GROUP. Published under the direction of the Director of Medical Services, 21 Army Group, with introduction by the Consulting Surgeon. 1945.

HIPPOCRATIC WISDOM FOR HIM WHO WISHES TO PURSUE PROPERLY THE SCIENCE OF MEDICINE. By William F. Petersen, M.D. Springfield, Illinois: Charles C Thomas, 1946.

APPLIED PHYSIOLOGY. By Samson Wright, M.D., F.R.C.P. London, New York, Toronto: Humphrey Milford, Oxford University Press, 1945.

KETTLE'S PATHOLOGY OF TUMOURS. By W. G. Barnard, F.R.C.P., and A.H.T. Robb-Smith, M.A. (Oxon.), M.D. (Lond.). 3 ed. New York: Paul B. Hoeber, Inc., 1946.

SESIONES QUIRURGICAS PARA GRADUADOS, HOSPITAL RAWSON. By Ricardo Finochietto. Lecciones de cirugia. First and Second Series. Buenos Aires: La Prensa Medica Argentina, 1945.

HIPERTIROIDISMO; FISIOPATOLOGIA Y TRATAMIENTO. By Jose Alberto Caeïro. Buenos Aires: Lopez & Etchegoyen S.R.L., 1945.

PAGINAS DE CIRUGIA. By Enrique Finochietto. Buenos Aires: La Prensa Medica Argentina, 1945.

ORAL MEDICINE; DIAGNOSIS—TREATMENT. By Lester W. Burket, D.D.S., M.D. With a Section on Oral Aspects of Aviation Medicine by Major Alvin Goldhush, D.D.S., M.S., D.S., A.U.S. Philadelphia, London, Montreal: J. B. Lippincott Co., 1946.

AMBULATORY PROCTOLOGY. By Alfred J. Cantor, M.D. With a foreword by Beaumont S. Cornell, M.D. New York and London: Paul B. Hoeber, Inc., 1946.

CLINICAL CONGRESS OF AMERICAN COLLEGE OF SURGEONS

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PLANS DEVELOP FOR 1946 CLINICAL CONGRESS OF THE AMERICAN COLLEGE OF SURGEONS

THE announcement in the March issue of SURGERY, GYNECOLOGY AND OBSTETRICS of the definite plans for holding the 1946 Clinical Congress of the American College of Surgeons at the Waldorf Astoria in New York City from September 9 to 13, has been greeted with enthusiasm. A large meeting and exceptionally keen interest are assured. The four years without a Clinical Congress have been years impressively lacking in a focal point for intensive study of trends in surgery, and surgeons everywhere are eagerly anticipating the resumption of the annual meeting.

Progress does not stop when there is no Congress, of course, but the application of new techniques and ideas is delayed when there are no opportunities for the meeting of minds that a large international conference affords. The Clinical Congress makes a convenient annual milepost by which to calculate and to evaluate advances in surgery, and it provides a spur to progress through this function and through its inspirational influence.

Surgeons need the stimulation that comes from directly hearing of new developments from the lips of those who helped to initiate them. They need opportunities to ask questions, to participate in discussions, and to observe other surgeons at work, both in the local hospitals and on the motion picture screen. The latter teaching device in particular is becoming increasingly profitable and popular as more good medical films are produced, and at the Clinical Congress ample opportunity is provided for surgeons to view the newest and best pictures.

The Clinical Congress, as the previous article indicated, will be the usual five-day session, embracing forums on fundamental surgical problems, panel discussions, clinical conferences, symposia, demonstrations, films, scientific sessions, hospital conferences, exhibits, and the formal Presidential Meeting and Convocation. This year the Convocation will be a particularly momentous event, since in addition to the initiates of the current year, there will be present a great many of the accumulated total of 2,744 surgeons who were received into fellowship in absentia during the four war years in which no Congress was held. It will also be an occasion of reunion for the Fellows, both new and old, many of whom have been overseas on military duty much of the time since the Boston Congress in 1941.

The new officers of the College who will be installed at the Presidential Meeting and Convocation are Dr. Irvin Abell of Louisville, as President; Dr. Leland S. McKittrick of Boston, as First Vice President; and Dr. F. Phinizy Calhoun of Atlanta as Second Vice President. The Presidential Address will be given by Dr. W. Edward Gallie of Toronto, the retiring president.

Plans are progressing for making the programs of all of the scientific sessions, morning, afternoon, and evening, provide the most comprehensive delineation possible of advances in surgery and related sciences during the five years since the 1941 Congress. The various surgical specialties, ophthalmology, otorhinolaryngology, neurology, orthopedics, obstetrics, gynecology, urology, plastic surgery, and the others, will be covered specifically and also as they are related to general surgery. The four-day hospital conference will be devoted to all phases of transition period plans and problems. A detailed outline of the programs will be published in the next issue.

Advance registration and hotel reservations are urged upon all who plan to attend the Congress.

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SURGERY Gynecology and Obstetrics

With International Abstract of Surgery

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PROTEIN

and the Dietary of Kidney Disease

The fundamental concept, that nutritional requirements must be met in disease as well as in health, holds especially true in renal disease.[1] Because many affections of the kidney involve excretion of blood albumin via the urine, the intake of protein in former years was curtailed in a futile attempt to stem the loss of protein.

Modern nutritional science has emphasized the necessity for maintaining nitrogen balance even in the face of the severe albuminuria characteristic of lipid nephrosis.[2] Not only must the basic nitrogen requirements of the organism be met, but the urinary loss must be compensated for as well.[3] Only when this adjustment of protein intake is made can the plasma albumin be restored to normal levels and the associated edema overcome.

Meat is an excellent source of protein in the management of nephritis and nephrosis, not only because of the high percentage of protein contained, but especially because its protein is of highest biologic quality, applicable for every protein need.

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[1] *Stare, F. J., and Thorn, G. W.: Protein Nutrition in Problems of Medical Interest, J.A.M.A. 127:1120 (April 28) 1945.*

[2] *Stare, F. J., and Davidson, C. S.: Protein: Its Role in Human Nutrition; Introduction, J.A.M.A. 127:985 (April 14) 1945.*

[3] *Anderson, G. K.: The Importance of Protein in Diet Therapy, J.Am.Dietet.A. 21:436 (July-August) 1945.*

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